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CONTENTS

Local Paralysis in Children after Injections. A. K. MARTIN . . 1
Sixth International Congress of Paediatrics 14
Muscle Spasm in Poliomyelitis. F. E. CARMODY and D. S. MALCOLM . . 15
A Survey of Recent Developments in the Treatment of Pneumococcal Meningitis. P. H. JACKSON 22
Protein Requirements of Infants (2). W. F. YOUNG, P. POYNER-WALLIS, H. [illegible], E. FINCH and I. BROADHURST . . 31
Neuro-muscular Incoordination of Respiration in the Newborn. JOSEPH [illegible] . . 32
Haemolytic Disease of the Newborn. L. ALBERT CLAIREAUX . . 61
Hypertension of Renal Origin in Childhood. A. I. GRIFFITHS . . 81
Epulis in the Newborn. F. A. LASSELY and A. DAVSON . . 89
Letterer-Siwe Disease. A. M. MACKELVIE and W. WALLACE PARK . . 93
Case Report:
Meconium Ileus with no Pancreatic Abnormality. E. HINDEN . . 99

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LOCAL PARALYSIS IN CHILDREN AFTER INJECTIONS

BY

J. K. MARTIN, M.B., B.S., M.R.C.P., D.Obst.R.C.O.G., D.C.H.
From the Department of Child Health, Guy's and Evelina Hospitals, London

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This paper has been written to draw attention to the association between intramuscular injections and flaccid paralysis of one limb. Seventeen affected children have been examined and followed up personally. The records of a further 60 to 70 cases have been available and have been used to provide information not clearly brought out in the shorter series. Cases in which injection preceded paralysis by more than 28 days have been excluded. The aetiology of the paralysis and the relationship it bears to the injection are discussed.

Clinical Features

Table 1
Analysis of Incidence in Relation to Age (in Years)

6/12-1	1-1½	1½-2	2-3	Total
7	7*	1	2	17

* Includes two cases following penicillin injections.

The average age of this group was one year, the youngest child being seven months, and all the children were under three years. In a further 39 cases occurring between 1941 and 1949 in which the age incidence was known, the average age was 4½ years and ranged from 9 months to 14 years. The higher age incidence was accounted for because children of school age represented the largest numbers of those inoculated in the early days of the immunization campaign. Taken as a whole the age groups reflect the average age at which immunization is carried out.

Taking all known cases, girls were slightly more frequently affected than boys.

Incubation Period. The average time between the injection and the onset of the paralysis was 16 days, the majority of cases occurring between 7 and 21 days, the shortest being 3 days and the longest 26 days.

Prodromal Symptoms. In this series there were without exception constitutional disturbances either preceding or at the time of onset of the paralysis. Nine patients had a history of fretfulness, lethargy, loss of appetite, or pyrexia within one to four days of becoming paralysed. In the remaining eight patients an 'upper respiratory infection,' pyrexia, or fretfulness occurred at some time following inoculation. Neck rigidity was found in four and pyrexia in five patients seen at the time of onset.

Pain and tenderness was not apparent either preceding or accompanying the paralysis. As all these children were under three years of age this does not of necessity entirely exclude its presence.

Paralysis. The onset was sudden, with a flaccid paralysis of the whole limb as a rule, but frequently sparing the fingers and toes.

The frequency with which an upper limb was affected, and in particular the left, would appear to reflect the commonest site for inoculation, namely the left deltoid muscle. The left arm was paralysed four times as frequently as the right, taking all known cases.

There was no affection of the cranial nerves and in only two cases (Cases 11 and 14) was any paralysis noted other than in the limb involved, and then it was only of a transient nature. Sensation, as gauged by pin prick, appeared to be normal.

The muscles involved in the arm were of constant distribution, namely, the supraspinatus, rhomboids, infraspinatus, teres minor, biceps, brachialis, deltoid, supinator longus, serratus magnus, pectoralis major, teres major, latissimus dorsi, triceps, and the extensors of the wrist and fingers. This distribution corresponds to the muscles supplied by the motor roots of the fifth, sixth, and seventh cervical segments of the spinal cord. The corresponding tendon reflexes were absent.

In the legs the muscles most constantly involved were the quadriceps and the anterior tibial group. Two cases at the onset showed complete flaccid paralysis of the leg except for some movement in the toes.

Course and Prognosis

The sequence of events in those cases involving an arm which recovered was for the wrist extensors to begin to act within a few days. The rhomboids, serratus magnus, teres major, and usually the teres

minor and the pectorals, recovered early. The biceps group and then the triceps group began to function next, about two to three months after the onset. The deltoid and spinati were the last muscles to recover, often taking a year or more. Considerable wasting of the affected muscles occurred. Of the 12 cases recorded in detail, two (Cases 2 and 11) have not been followed up for a sufficient length of time to give a prognosis. Of the remainder, Case 12 has made an almost complete recovery, there being a little residual weakness in the deltoid only. Four others (Cases 1, 5, 6, 10) have made good partial recoveries, and of these at least two will probably be complete. The other five cases include one (Case 9), in which there has been virtually no improvement after 18 months, and four (Cases 3, 4, 7, 8) in which the shoulder girdle and upper arm muscles have remained paralysed after a year. Some improvement in the muscles of the upper arm in these cases might be anticipated. A study of further records tended to confirm that about 50% made a good functional recovery.

As in anterior poliomyelitis the prognosis is difficult to assess in the early stages and recovery can start 9 to 12 months after the onset, continuing up to two years or possibly longer.

In the cases in which a leg was involved none made a complete recovery in periods of up to 18 months. Of the two cases (Cases 13 and 16) in which initially the whole of one lower limb was paralysed, one patient is left with no action of the quadriceps and tibialis anterior after nine months, and the other still has extensive paralysis after six months. Of the other three a good partial recovery has occurred in one, and in two slight improvement only.

Investigations

Lumbar Puncture. The cerebrospinal fluid was examined in seven cases. The other cases were not seen until too long after the onset to justify such a procedure. In the cases mentioned, details of which are given in Appendix A, the changes included a raised cell count and serum protein level and were consistent with those found in poliomyelitis.

Schick Test. This had been done on only one patient, who proved to be Schick-positive and was given two further immunizing doses without untoward effects.

Examination of Stools for Poliomyelitis Virus. Animal inoculation from Case 11 was tried, but the result was negative.

Electrical Reactions. Electrical testing of the affected muscles showed the reaction of degeneration. As in other lesions of the lower motor neurone type these reactions are probably of more value in prognosis than diagnosis.

Treatment

Treatment similar to that employed in poliomyelitis was used. Paralysed muscles were splinted, and cases involving an arm were put up in an ' aeroplane ' abduction splint. The most important part of physical treatment was to remove all splinting at least twice a day and put the joints through a full range of movement. As soon as any voluntary power returned graduated active movements were given. At this stage the child was encouraged to use the limb as much as possible during certain periods of the day. Galvanism was used in some cases in which the reaction of degeneration was obtained in order to maintain muscle bulk (Gutmann and Guttmann, 1944). Where possible, patients attended a physiotherapy department three or more times weekly.

Details of Injections Used

There appears to be no relationship between the substance inoculated and the paralysis. Materials used included A.P.T., pertussis vaccine alone or combined, and T.A.F. Other writers (Walshe, 1945; Parsonage and Turner, 1948) report the occurrence of paralysis after T.A.B., tetanus toxoid, and antityphus vaccine, but these cases were probably of a different aetiology. In this series there are two cases following penicillin given as treatment for boils and stomatitis respectively. The material injected was produced by at least six different manufacturers. In several cases a specimen from the same batch of material was obtained and returned to the manufacturers for detailed examination without any harmful agent being found. Cases occurred after the first, second, or third immunizing dose.

No local reactions occurred in this series.

Apart from the constitutional symptoms mentioned, only one patient (Case 11) became pyrexial immediately after inoculation, and in this patient the paralysis developed within three days. In the remainder no immediate generalized reactions and nothing akin to serum sickness developed.

Epidemiology

It is a little difficult to draw any conclusions from such a small series as shown in Table 2, particularly when it is realized that cases were chiefly sought in the years 1946-1949. Taking a larger series of 67 cases (Table 3) there is suggestive evidence that these cases occur chiefly when there is a high prevalence of poliomyelitis.

TABLE 2

ANNUAL INCIDENCE OF PRESENT SERIES

Year	No. of Cases of Paralysis
1944	1
1945	2
1946	0
1947	5*
1948	8†
1949	1 (first six months)

* One penicillin case.
† For both 1947 and 1948.

TABLE 3

INCIDENCE OF PARALYSIS AFTER INJECTION COMPARED WITH POLIOMYELITIS AND POLIO-ENCEPHALITIS (NOTIFICATIONS) FOR ENGLAND AND WALES

Year	Cases of Paralysis	Notifications
1941	10	959
1942	6	674
1943	5	456
1944	6	532*
1945	9	858*
1946	0	673*
1947	18	7,766*
1948	12	1,840*
1949	12 (first nine months)	

* Corrected.

TABLE 4

SEASONAL INCIDENCE OF 17 CASES

Month	No.	Month	No.	Month	No.	Month	No.
Jan.	0	April	0	July	3	Oct.	1
Feb.	0	May	1	Aug.	5	Nov.	2*
Mar.	1	June	2	Sept.	1	Dec.	1
Totals	1		3		9		4

* Include one case following penicillin injection.

The maximum seasonal incidence is seen to be in the summer and autumn months with sporadic cases practically throughout the year. This is amply confirmed by taking the records of all cases known (70-80 cases) when it was found that just over 50% occurred between July and September and about 30% in October-December. This seasonal incidence corresponds closely to that of poliomyelitis.

Association with Cases of Poliomyelitis. In only two cases out of 17 was a history of poliomyelitis in the same district obtained; in one of these it occurred in another member of the family. Detailed enquiry from local health authorities regarding poliomyelitis in the corresponding districts was not made. There is, however, some suggestive evidence in the records of the larger series studied that groups of cases occurred in areas in which there was a high incidence of poliomyelitis at the time.

Discussion

The diagnosis made in almost every case studied was that of poliomyelitis. In general no enquiry as to recent inoculations or injections was made until a later date. The question remains to be answered whether the relationship between an inoculation and subsequent paralysis is fortuitous, as these children were in a common age group for both immunization and poliomyelitis. The true incidence of such an association is difficult to obtain. A study of two sets of poliomyelitis records, taken at random, was made in different hospitals. In one series of 80 cases of poliomyelitis, three were found in which a paralysis of one limb occurred within a month of inoculation. In the other series of 56, seven such cases were discovered. No survey of large numbers of recently immunized children has been made to see if any became paralysed. A possible source of evidence has been obtained from the survey of poliomyelitis in England and Wales in 1947 organized by the Public Health Laboratory Service (McFarlan, 1949), which disclosed that there were 495 cases in children under the age of ten years. In 14 of these a definite history was obtained of immunization against diphtheria or pertussis within one month of paralysis. Eleven of these cases occurred in 308 poliomyelitis cases aged under five years, i.e. in the common age group for inoculation. Brain (1943) discussing the neurological sequelae of inoculations refers to three cases of poliomyelitis following diphtheria toxoid occurring when the disease was already prevalent. He points out that the relationship of the infection to the inoculation is at present unsettled and that before deciding it exists it is necessary to ascertain statistically that the incidence is higher among immunized children than in the community at risk. In any case, when the number of inoculations given is considered these complications are obviously rare.

Various factors suggest themselves as being of possible aetiological significance.

Toxins or Virus Introduced with the Injection. The possibility of toxins or virus contaminants contained in the material injected was considered. Under the Therapeutic Substance Act Regulations products of this nature are not allowed to be issued if they contain any free toxins. 'Batch' samples returned to the manufacturers were injected into

animals and no specific reactions were observed. They were also found to be sterile on culture.

The possibility of contamination is remote even with a virus, and if it did occur the makers state that the virus would be inactivated during the manufacturing process. Furthermore, no two cases of paralysis occurred in which the same batch or even the same bottle of material was used. Introduction of a virus at the time of injection has to be considered. A few enquiries indicate that a fresh needle is used for each injection, though the same syringe is employed several times. If a virus were introduced from the syringe in the same way as serum hepatitis occurs, one would expect multiple cases from one inoculation session rather than isolated examples, as in fact occurred. Moreover it has yet to be shown that such a virus causing paralysis can be conveyed from one human being to another in this way. It would be reasonable also to expect more cases to occur after any other intramuscular injection. Hughes (1944) has suggested, but without any direct evidence, that cases following injections of serum might be due to a virus thus introduced.

Allergy. With regard to the question of the tissues being sensitized by an initial injection, one would expect, if this were so, that all cases would occur after the second or third injection. In fact, in this series, six out of the 17 patients were paralysed following the first injection. Of a further 40 cases in which details are known this occurred in eleven.

Reactivation of a Latent Virus within the Tissues. Again the condition should be very much commoner after any other intramuscular injection unless there is something specific in immunizing agents which reactivates a dormant virus. Keim (1939) and Keim and Wakefield (1940) discuss such possibilities with some favour. Such a theory in the present state of knowledge is unattractive on the grounds that it is difficult to verify.

Brachial Neuritis. Neurological complications following the administration of serum have been recognized for some time (Allen, 1931; Smith 1939; and other workers). Allen gives a good description. Injection of serum was followed by an attack of serum sickness within five to ten days. Two to five days later, or if serum sickness did not occur within two to five days of its expected date, one of four possible sequelae was seen: paralysis of a radicular type (Cases 5 and 6) accompanied by much pain (sensory loss was rare but where present it involved the outer aspect of the upper arm); neuritic; polyneuritic; or cerebral disturbance. Lumbar puncture was not performed in these cases. The pathogenesis postulated was oedema of the nervous tissue occurring during the serum sickness. More recently a number of writers have reported series of cases, particularly in the Near East, of 'brachial neuritis' (Parsonage and Turner, 1948; Spillane, 1943; Wyburn-Mason, 1941; Dixon and Dick, 1945; Turner, 1944). One of the best descriptions is given by Parsonage and Turner under the title 'neuralgic amyotrophy,' the shoulder girdle syndrome. Only a certain proportion of their cases were of the same distribution as the 12 mentioned in this series. Moreover, they differ in the accompaniment of severe pain, some sensory loss, and in particular the absence of constitutional symptoms and changes in the C.S.F. In many papers cases which were preceded by injections or trauma are excluded. Paul *et al.* (1944) tried to isolate poliomyelitis virus from the faeces of six cases of the syndrome and were unsuccessful, but obtained the virus from nine out of fifteen cases of poliomyelitis. Parsonage and Turner conclude that the complete clinical similarity between their cases and the serum cases make it reasonable to assume that they are of similar aetiology, although this remains unknown. Spillane (1943), discussing trauma and injections as aetiological agents, excludes the former on history, and the latter on similar grounds and on the fact that the majority of his cases involved the right arm and injections are usually given in the left. In the vast majority of cases in this series paralysis affected the left arm into which inoculations are most commonly given.

There is comparatively little in the literature giving examples following immunization similar to those recorded in this paper. Walshe (1945) under the heading 'brachial neuritis' makes reference to it occurring after tetanus antitoxin, diphtheria antitoxin, T.A.B., etc. His description of these cases is similar to that of other writers mentioned above. Pain is a prominent feature, paralysis is often bilateral and involves chiefly the deltoid, serratus anterior, rhomboids, spinati, and triceps; sensory loss is minimal and may be absent. No mention is made of constitutional symptoms or changes in the cerebrospinal fluid. In the series described by Parsonage and Turner enquiry was made regarding recent vaccination and inoculations in 67 patients. Of these 11 had had inoculations during the four weeks preceding the onset of their shoulder girdle symptoms, which included T.A.B., tetanus toxoid, and typhus vaccine (European). Clinically these cases differed from my series in the manner already described. Turner (1944) in describing 36 cases of 'brachial neuritis' states that there is nothing comparable to it in the legs.

Anterior Poliomyelitis. The distribution and course of those cases of paralysis as it affected the

leg are sufficiently similar to poliomyelitis to need no further comment. The virtually segmental distribution of paralysis affecting the arm appears at first sight a little unlike infantile paralysis, but a study of poliomyelitis records suggests that it can occur. The muscles most commonly affected (Wilson 1940) are the deltoid and upper arm muscles.

Wilson (1940) recording the findings of four authors in different epidemics gives the age incidence as 6-15% occurring under one year, and 42-75% occurring between one and four years. Comparable figures taken from two series of records at different hospitals in this country between 1946 and 1949 show an incidence of 6% and 11% under one year, and of 37% and 44% between one and five years.

That poliomyelitis may affect only one limb is shown in an analysis made by Lovett (1916). In 1,166 cases one leg was affected in 25·9% of cases and one arm in 7·1%. Taking two random samples of poliomyelitis from hospital records in this country, there were 56 cases, of which 7 followed within a month of inoculation in one instance, and 80 cases, which included 3 following inoculation in the other series. Omitting the post-inoculation cases, in 8% one arm was involved and in 30% one leg, which is in accord with most figures published for poliomyelitis epidemics. Such figures indicate the predominance of leg paralysis compared with the arm, and are in contrast to the cases following inoculation in which the arm is most commonly afflicted. If in the two series mentioned the post-inoculation figures are included, the percentages work out at 7% arm paralysis, 7% arm paralysis after inoculation, and 28% leg paralysis. The percentage of arm cases is seen to be practically doubled and the ratio of leg to arm falls from 4 to 1 to 2 to 1. Such a comparison may not be statistically significant, and of course inaccuracies arise, as inoculations are not by any means always recorded in the case histories of poliomyelitis. Nevertheless it does suggest that inoculation may determine the site of paralysis. The analogy of the relationship between tonsillectomy and poliomyelitis immediately occurs. It is recognized that tonsillectomy does not increase the chances of infection, but if a person is to get the disease the chances of it being of the bulbar variety become extremely high (Horstmann, 1948).

Further ideas along these lines are given by Russell (1949) in an article on paralytic poliomyelitis. In discussing the effect of trauma he quotes Levinson *et al.* (1945) as having reported a few cases in which local trauma appeared to determine the site of maximum paralysis. That peripheral trauma provides the virus with easy access to the neurones, or that it modifies the physiology of the spinal cord cells of the segments concerned in such a way as to make them more vulnerable to the virus, he suggests as possibilities. Two cases of paralysis following T.A.B. and penicillin injections respectively are reported. Commenting on these it is postulated that the trauma of injection might possibly increase the vulnerability of that part of the spinal cord which supplies the site of injection.

Prophylaxis

Despite the fact that the relationship between inoculation and subsequent paralysis has not been proved statistically, the association, though uncommon, would appear to be of sufficient importance to make one consider prophylactic measures. Further, if the public comes to associate inoculation with the possible risk of paralysis, the immunization campaign may thereby fall into some disrepute. In view of this possibility, taken in conjunction with the seasonal incidence, it might well prove wise to suspend inoculations during part of the year, or in areas where poliomyelitis is prevalent. It is admitted that any measure affecting the immunization campaign must be given most careful thought lest more harm than good ensue.

Summary

Seventeen cases are described in which paralysis of a single limb has occurred within 28 days of receiving an injection. Of these fifteen followed immunization and two penicillin.

The aetiology is discussed. The facts pointing to poliomyelitis are the constitutional symptoms, the changes in the cerebrospinal fluid, and the seasonal incidence.

The question of the trauma of an injection determining the site of maximum paralysis is discussed.

It is concluded that there is a case for considering the suspension of immunization during an outbreak of poliomyelitis.

I am indebted to the medical staffs of the Hospital for Sick Children, Great Ormond Street, and the Evelina Hospital for Sick Children for permission to publish their cases; to the medical superintendents of the Western Fever Hospital and Queen Mary's Hospital, Carshalton, for giving me access to their poliomyelitis files; to Dr. A. H. Gale, of the Ministry of Health, for helpful advice and reports on additional cases; and to Dr. P. R. Evans for criticism and encouragement.

APPENDIX A

Case No. and Sex	Age	Site and Type of Inoculation	Dates Given	Onset	Incubation Period
1. A.W. Male	$1\frac{4}{12}$ years	Left arm A.P.T. and pertussis (0·5 ml.) " " " (0·5 ml.) " " " (0·5 ml.)	27.5.48 24.6.48 22.7.48	13.8.48 Off colour one day before paralysis	22 days
2. M.G. Female	10½ months	Left deltoid Pertussis (0·5 ml.) A.P.T. (0·2 ml.) Pertussis (0·5 ml.) A.P.T. (0·2 ml.)	About 12.8.48 About 12.9.48	12.10.48 ' Cold ' with running nose 7 days before onset. Another case of A.P.M. in vicinity	28 days
3. J.M. Male	10 months	Arm Pertussis (0·5 ml.) A.P.T. (0·2 ml.)	6.5.48	14.5.48 Feverish and miserable after the onset	8 days
4. P.H. Female	7 months	Left arm Pertussis (0·5 ml.) " (0·5 ml.) " (0·5 ml.)	23.1.47 6.2.47 20.2.47	8.3.47 Drowsy on 2.3.47. Fretful on 8.3.47	16 days
5. M.P. Female	$2\frac{10}{12}$ years	Left arm A.P.T. (0·3 ml.)	16.7.48	31.7.48 Upper respiratory infection and tonsillitis. 18.7.48 Fretful and lethargic	15 days
6. J.C. Female	6½ months	Left arm A.P.T. (0·2 ml.) A.P.V. (0·5 ml.)	16.7.45	Head cold on 30.7.45	26 days
7. D.J. Male	1 year	Left arm A.P.T. A.P.T.	End of Sept. 25.10.45	11.11.45 Day before onset child was fretful and refused to eat	17 days
8. G.J. Male	10 months	Left arm A.P.T. and pertussis (0·5 ml.)	28.7.48	15.8.49 Feverish and fretful for 2 days before onset. Vomiting	18 days
9. K.G. Male	1½ years	Two injections against diphtheria	End of May, 1947	11.6.47 Coryza 10 days before onset; lasted 3 days. Then off food. Feverish, miserable, and no appetite 3 days before onset	7–14 days

Case No. and Sex	Age	Site and Type of Inoculation	Dates Given	Onset	Incubation Period
10. M.J. Female	2¼ years	A.P.T.	Aug., 1947	5.9.47 Three weeks before onset had 3 fits in one day. Associated with coryza which lasted one week	2–3 weeks
15. C.S. Female	15 months	Left arm A.P.T. (0·5 ml.) A.P.T. (0·5 ml.)	 20.5.49 17.6.49	20.6.49 T. 103° on night of injection. Next day arm weak. June 20 left arm paralysed. June 21 or 22 neck stiffness noted	3 days
12. J.F. Female	1 10/12 years	Left buttock A.P.T. A.P.T.	 Unknown 20.6.48	11.7.48 Pyrexial for 4 days before onset	21 days
13. J.H. Female	1 year	Right buttock A.P.T. and pertussis	 28.7.48	7.8.48 Fretful, feverish and drowsy for 48 hours before onset. Leg tender but no local inflammation	10 days
14. M.L.	18 months	Buttock A.P.T. A.P.T.	 3.7.47 31.7.47	Aug., 1947 Pyrexia 7 days after inoculation. Three days later both legs weak, left worse than right. Latter recovered in 2 days	10–14 days
15. J.B. Female	16 months	Both arms A.P.T. A.P.T.	 Oct., 1944 28.11.44	12.12.44 ' Off colour ' for 2 days before paralysis	14 days
16. J.H. Female	18 months	Buttocks Five injections of penicillin for boils (100,000 units b.d.)	 15.10.48 16.10.48 17.10.48	3.11.48	16 days
17. M.G. Female	14 months	Buttocks Four injections of penicillin for ' ulcerated throat '	 20.6.47 21.6.47 22.6.47	5.7.47 Some difficulty in walking. 2.7.47. Bad tempered and vomiting. Pyrexial 28.6.47	13 days

APPENDIX B

Case No.	Clinical Examination	Reflexes
1	27.8.48. Cranial nerves, legs and right arm normal. *Left arm* hangs by his side. Flaccid paralysis. Deltoid, spinati, biceps, brachialis, triceps no contraction. Pectoralis major acting. Flexors and extensors of wrist acting well. Uses hand. Good grip.	Triceps, biceps and supinator jerks on the left absent. Other tendon reflexes normal. Flexor plantar responses.
2	16.10.48. Cranial nerves, legs and right arm normal. *Left arm*, trapezius acting. Supraspinatus, infraspinatus, teres major, teres minor not tested satisfactorily. Pectoralis major, rhomboids, serratus anterior and latissimus dorsi appeared to be acting. Deltoid, triceps and biceps paralysed. Extensors of wrist weak. Flexors of wrist and small hand muscles appear to be acting.	Triceps, biceps and supinator jerks on the left absent.
3	9.8.48. Widespread flaccid paralysis of *right shoulder girdle* and arm. Marked wasting of deltoid. Cranial nerves normal. Legs and left arm normal.	Triceps, biceps, and supinator jerks absent on the right. Other tendon reflexes normal.
4	10.3.47. Temperature 99. Would not move head or sit up. Flaccid paralysis of *left arm* including the shoulder girdle, biceps and triceps groups, flexors and extensors of the wrist. Some movement of the fingers.	
5	4.8.48. Onset of flaccid paralysis of left arm. Four days before being seen as an out-patient cranial nerves, legs, and right arm, normal. *Left arm.* Shoulder girdle muscles, triceps, biceps, brachialis no contraction. Extensors and flexors of wrist, small muscles of hand, no abnormality detected. No wasting or fibrillation. No tenderness or pain.	Biceps, triceps and supinator jerks absent on the left. Other reflexes normal.

Electrical Reactions	C.S.F.	Follow-up
30.8.48. Deltoid, triceps, pectoralis major, rhomboids, infraspinatus, teres major and minor showed no response to faradism. Biceps gave a flicker. Trapezius, serratus anterior fore-arm muscles, and small muscles of the hand responded to faradism.	—	15.9.48. Biceps and brachialis now acting. Supinator jerk (left) obtained. 29.9.48. Triceps now acting. Rhomboids normal. 19.10.48. Spinati wasted. Flicker in deltoid. Biceps jerk present. 11.3.49. Raises arm above head. Only muscle completely knocked out, infraspinatus.
22.10.48. Deltoid gave no response to faradism. Triceps, biceps, rhomboids, latissimus dorsi, pectoralis major, and serratus anterior gave very weak response. Remaining muscles gave good response.	16.10.48. Clear-cells, 17 per c.mm. Protein, 30 mg. Sugar, 40. Chlorides, 720. Culture sterile. 27.10.48. Clear-cells, 1 per c.mm. Protein, 45 mg. Sugar, 59. Chlorides, 740.	18.10.48. Weak action of biceps. Forearm muscles and hand much stronger. 1.11.48. No contraction of deltoid, moving arm more freely. 'Trick' movements at shoulder. Supinator jerk obtained. Biceps and triceps still absent.
11.8.48. Rhomboids, teres, latissimus dorsi, serratus anterior, pectoralis major, deltoid, biceps, triceps, extensor indicis, extensor communis digitorum, extensor ulnaris, extensor carpi radialis longus and brevis—no response to faradism. Opponens pollicis, abductor pollicis brevis—no response to faradism. Trapezius gave a good response to faradism. Extensor pollicis longus, abductor pollicis brevis, extensor minimi digitis, flexors of wrist and small muscles of hand gave weak response 5.8.49. Biceps and triceps gave a weak flicker on faradic stimulation.	—	10.1.49. Beginning to use hand. 20. Small muscles of hand, flexors and extensors of wrist now acting well. ? flicker in triceps. Biceps group, deltoid, spinati, pectorals, no action. 5.8.49. Flexors of wrist and hand 5. Extensors of wrist 4. Biceps and triceps 0. Deltoid and spinati 0. Pectorals, teres major, latissimus dorsi—flicker. Trapezius 5.
20.9.48. Trapezius, pectoralis major, flexors and extensors of wrist, small muscles of hand gave a good response to faradism. Teres major, spinati, rhomboids, biceps and triceps gave a sluggish response to faradism. Serratus anterior and deltoid gave no response to faradism.	—	12.4.47. Lifting head. Flexors and extensors of wrist, small muscles of hand acting well. Deltoid, spinati, biceps and triceps wasted and not acting. 20.9.48. Flexors and extensors of wrist, small muscles of hand acting well. Deltoid, spinati, biceps and triceps not acting. Trapezius, pectoralis major, rhomboids, teres major acting.
—	—	23.9.48. Trapezius, serratus anterior, pectoralis major acting, spinati, deltoid, triceps; paralysed and wasted. Biceps and brachialis, some wasting, weak contraction 3. Reflexes, weak supinator jerk. 28.10.48. Deltoid and spinati remain wasted. Triceps 3. Biceps 4. 24.2.49. Much improved. Can now use deltoid and raises arm above head.

Case No.	Clinical Examination	Reflexes
6	15.8.45. Cranial nerves, transient left facial weakness noted. Legs and right arm normal. *Left arm*, complete flaccid paralysis. No wasting.	Biceps, triceps, supinator jerks absent on the left. Other tendon reflexes normal. Flexor plantar responses.
7	14.11.45. Temperature 100·4° F. Flushed. No neck rigidity. Flaccid paralysis of *left arm*, including shoulder girdle muscles, biceps, triceps, and fore-arm muscles. Cranial nerves, legs and right arm normal.	Biceps, triceps and supinator jerks absent on the left. Other tendon reflexes normal. Flexor plantar responses.
8	15.8.48. Temperature 100° F. Neck rigidity. Cranial nerves, right arm and legs normal. *Left arm*, flaccid paralysis of shoulder and arm muscles. Extensors and flexors of wrist, small muscles of hand acting.	Biceps, triceps, supinator jerks absent on the left. Other tendon reflexes normal. Flexor plantar responses.
9	12.6.47. Temperature 100° F. Some neck rigidity. Cranial nerves, right arm, and right leg normal. *Left arm*, flaccid paralysis of muscles of left shoulder and arm. Moves wrist and hand. Some weakness of flexors and extensors of wrist and muscles of hand.	Triceps, biceps, supinator, knee jerks absent on the left. Other tendon reflexes normal. Flexor plantar responses.
10	5.9.47. Temperature 100·6° F. No neck rigidity. Cranial nerves, left arm, and legs normal. *Right arm*, trapezius functioning. Flaccid paralysis of shoulder girdle muscles, biceps, triceps. Flexors and extensors of wrist, small muscles of hand normal.	Triceps, biceps jerks absent on the right. Other tendon reflexes normal.
11	25.6.49. Apyrexial. No neck rigidity. Cranial nerves, right arm normal. Legs, some loss of power in legs, right more than left. *Left arm*, flaccid paralysis of left shoulder girdle and arm muscles. Muscles of fore arm weak. Moving hand.	Triceps, biceps, supinator jerks absent on the left. Other tendon reflexes normal. Flexor plantar responses.

Electrical Reactions	C.S.F.	Follow-up
30.6.47. Entirely normal except for some weakness of response of triceps. 30.6.47. X-ray, small bilateral cervical ribs.	15.8.45. Clear fluid. Cells 3 per c.mm.	17.6.47. Marked wasting of all muscles of left arm. Slight wasting of thenar eminence. Shoulder girdle, muscles with the exception of deltoid and spinati appear to act well. Voluntary movement in left arm quite good. Picks up objects with hand. Grip weak. 27.10.48. Residual weakness of deltoid and triceps. Some wasting of muscles of forearm. All movements full and free. All tendon reflexes obtained. 19.8.49. Left arm smaller than right with one inch of shortening of forearm. Deltoid 4. Triceps 3. Other muscles acting well.
8.12.46. Pectorals, scapular muscles, no response to faradism, flicker to galvanism. Deltoid, biceps, triceps, no response to faradism. Weak galvanic response. Extensors and flexors of wrist appeared to respond normally. Child uncooperative.	15.8.45. Turbid fluid. Protein, 15 mg. Cells, R.B.C., 2,500; Sugar, 65; Chlorides, 740. Culture sterile.	16.5.46. Marked weakness of all muscles of left shoulder and arm. 12.7.46. Paralysis of shoulder girdle, deltoid, biceps and triceps. Wrist and hand muscles functioning well. 6.12.46. No change, marked wasting of affected muscles.
17.11.48. Deltoid, biceps, and triceps showed the reaction of degeneration.	16.8.48. Clear, colourless fluid; W.B.C., 50 per c.mm. (predominantly lymphocytes); R.B.C., 10 per c.mm. protein, 30 mg.; chlorides, 710; sugar normal. Culture sterile.	31.8.48. Some wasting of spinati. No movement at shoulder. Biceps and triceps group paralysed. 26.10.48. Pectorals, latissimus dorsi, trapezius 5. Deltoid and spinati 0. Triceps 0. Biceps 1. Fore-arm and muscles of hand 5.
—	13.6.47. Clear, colourless fluid. Cells, 8 lymphocytes; protein, 40 mg.; (negative Pandy); chlorides, 740; culture sterile. 18.6.47. Clear, colourless fluid. Cells, 1 lymphocyte and 3 R.B.C.'s; protein 50 mg.; chlorides, 730; culture sterile.	16.6.47. Muscle tone and reflexes in left leg normal. 29.8.47. Deltoid and abductors of shoulder 0. Biceps and Triceps 0. Extensors of wrist 2. Flexors of wrist 4-5. Grip 5. 4.2.49. Rhomboids, teres major, pectorals, latissimus dorsi 5. Spinati, deltoid, biceps, triceps 0. Supinatus and pronators 1. Extensors of wrist 2. Flexors of wrist, small muscles of hand 5.
—	5.9.47. Clear, colourless fluid. Cells, 30 polymorphs; 39 lymphocytes; 10 R.B.C.'s protein, 20 mg.; chlorides, 710; sugar present; culture sterile.	11.10.47. Triceps beginning to act. Otherwise no change. Tendon reflexes—weak triceps jerk obtained. 31.10.47. Immunized with A.P.T. and pertussis vaccine. Left arm. 27.11.47. Immunized with A.P.T. and pertussis vaccine. Left arm. 11.2.49. Rhomboids, pectorals, latissimus dorsi, teres major, serratus anterior 5. Spinati wasted, some action. Deltoid, wasted 0. Biceps group 4. Triceps 4. Fore-arm and hand 5. All tendon reflexes obtained.
—	25.6.49. Clear, colourless fluid. Cells, 19; protein, 50 mg.; sugar, 61; chlorides, 729.	Latissimus dorsi, rhomboids, trapezius, teres major 5. Pectorals appear to be acting. Deltoid, spinati, biceps and triceps 0. Extensors of wrist 4. Flexors of wrist and hand 5.

Case No.	Clinical Examination	Reflexes
12	12.7.48. Admitted to hospital. Cranial nerves, right arm and legs normal. Spinal muscles, some weakness. *Left arm*, flaccid paralysis of left shoulder girdle and arm muscles.	—
13	8.9.48. Cranial nerves, arms and left leg normal. *Right leg*, before onset of paralysis could stand, but not walk. Able to sit up. Flaccid paralysis of right hip girdle and leg muscles. Movement of toes only.	Ankle and knee jerks on the right absent. Other reflexes normal.
14	15.9.47. Cranial nerves, right leg and arms normal. *Left leg*, marked lordosis. Waddling gait, with left thigh externally rotated. No gross wasting. Foot drop.	Tendon reflexes normal.
15	15.12.44. Apyrexial. Walked at one year, now unable to do so. Cranial nerves, arms and right leg normal. *Left leg*, tenderness of muscles noted. Anterior tibial group paralysed.	Knee and ankle jerks absent on left. Other tendon reflexes normal. Flexor plantar responses.
16	4.11.48. Temperature 100·4° F. Not using right leg. Sitting up. Cranial nerves, arms and left leg, trunk muscles normal. *Right leg*, flaccid paralysis ; movement of toes only. Glutei, quadriceps, hamstrings, anterior and posterior tibials, peronei paralysed.	Knee and ankle jerks absent on the right. Other tendon reflexes normal. Flexor plantar responses.
17	5.7.47. *Right leg* giving way on walking.	

Electrical Reactions	C.S.F.	Follow-up
—	—	19.7.48. Able to raise hand. 9.8.48. Paralysis of left deltoid, trapezius, pectorals, latissimus dorsi, biceps and triceps reported. ? weakness of left leg. 19.10.48. Pectorals, latissimus, trapezius, rhomboids, acting well 5. Spinati and deltoid wasted and paralysed 0. Biceps group weak but contracting 2. Triceps acting well 4. Flexors and extensors of wrist, hand muscles acting well 5. 11.8.49. Slight residual weakness of deltoid only.
20.6.49. Erector spinae, fair response to faradism. Glutei, hamstrings, weak response to faradism. Adductors gave flicker but voluntary movement noted. Quadriceps, tibialis anterior, no response to faradism.	—	15.10.48. Flexion of hip by psoas and iliacus. Gluteus maximus, no contraction detected. Hamstrings acting against resistance. Quadriceps wasted and paralysed. Adductors very weak. Calf muscles, anterior tibials, and peronei acting weakly. Right ankle jerk obtained. 20.6.49. Standing but not walking. Glutei acting. Adductors weak. Quadriceps wasted and paralysed. Tibialis anterior appears paralysed. Calf muscles, tibialis posterior, peronei, flexors and extensors of toes gave good response to faradism.
22.1.48. Tibialis anterior and extensor digitorum gave no faradic response. Tibialis posterior and extensor hallucis gave weak faradic response.	—	22.1.48. Half-inch wasting of calf. Paralysis of tibialis anterior; ankle jerk sluggish. 9.1.49. Still no action of tibialis anterior.
6.2.47. Gastrocnemius, soleus, posterior tibial group gave no response to faradism. Quadriceps, hamstrings, anterior tibial gave good responses to faradism. Adductors and peronei gave a fair response.	—	March, 1945. Residual weakness of quadriceps and anterior tibial group. 23.8.45. Following 'measles' the posterior tibial group was noted to be weak. 6.5.46. Pes cavus with weakness of anterior tibial muscles. Calf muscles and posterior tibial weak. 20.1.47. As above, voluntary movement present but weak. Quarter inch shortening of leg. Calcaneo-cavo-valgus deformity.
—	—	12.4.49. Gluteus maximus, abductors, flexors and external rotators of hip 0. Adductors and internal rotators of hips 1. Quadriceps 0. Hamstrings 2. Calf muscles and peronei 3. Tibialis anterior 0. Tibialis posterior 1. Flexors and extensors of toes 3-4.
12.9.47. All muscles in right leg gave good response to faradism.	—	12.9.47. Half-inch wasting of thigh and calf. Limps with leg externally rotated. 25.1.49. Walks with a dip to the right. Some wasting of right buttock and half-inch wasting of right thigh. Three-quarter inch shortening of leg. Glutei, quadriceps, hamstrings, tensor fascia lata weak. Adductors acting well. Anterior and posterior tibial groups, peronei, flexors and extensors of toes full power. Tendon reflexes, weak knee jerk on right.

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SIXTH INTERNATIONAL CONGRESS OF PAEDIATRICS

The Sixth International Congress of Paediatrics will be held at the end of July, 1950, in Zürich, Switzerland. President, Professor G. Fanconi, M.D.

Programme

Friday, July 21. Opening of the scientific and industrial exhibition. Opening of the public exhibition, organized by the World Health Organization, the International Red Cross, and the International Union for Child Welfare.

Friday, July 21, and Saturday, July 22. Advanced lectures, partly intended as introduction to the group lectures.

Sunday, July 23. Official reception (evening).

Monday, July 24, p.m. to Thursday, July 27. Group lectures of which six to seven will be held simultaneously.

Thursday, July 27, p.m. Excursion on the Lake of Zürich.

Friday, July 28, a.m. Second Plenary Session.

Friday, July 28, p.m. Group lecture held jointly with the International Union against Venereal Disease.

Friday, July 28. Banquet.

Friday, July 28 and Saturday, July 29. Advanced lectures.

Monday, July 31 (evening). Close of the exhibition.

During the Conference there will be demonstrations and conducted tours through a number of laboratories, hospitals and welfare institutions. Tours of historical interest will be arranged and also a special programme for ladies.

Last Date for Registering

The date for registering for the Congress has been deferred to *Saturday, April 22, 1950*, and registrations must be made with the American Express Co. Inc., Sihlporteplatz 3, Zürich, or their agencies or correspondents in the different countries.

Congress Cards

Each participant in the Congress must be in possession of a congress card which is available at the agencies and correspondents of the American Express Co. Three different types of congress cards will be issued.

Congress Card Serie " A ", Sw. frs. 100. This entitles the holder to participate in all sessions, visits and receptions, including the official reception, the official banquet, and the excursion on the Lake of Zürich; also to free admission to the scientific and industrial exhibition, and receipt of all printed Congress literature.

Congress Card Serie " B ", Sw. frs. 60. This card is for accompanying ladies. It entitles the holder to participate in all sessions, visits, and receptions; to free admission to the scientific and industrial exhibition; and to take part in the entertainments provided in the ladies' programme.

Congress Card Serie " C ", Sw. frs. 60. This entitles the holder to participate in all scientific sessions, to free admission to the scientific and industrial exhibition, and to receipt of all printed Congress literature.

Hotel Accommodation

Applications for hotel accommodation have to be made with the agencies or correspondents of the American Express Co. Arrangements can also be made through the American Express Co., for those travelling under restricted financial allowances, to obtain cheaper accommodation, i.e. bed, breakfast, and one meal at Sw. frs. 10. per day.

MUSCLE SPASM IN POLIOMYELITIS

A STUDY OF A NEW ZEALAND EPIDEMIC

BY

J. E. CAUGHEY, M.D.(N.Z.), F.R.C.P., F.R.A.C.P., and
D. S. MALCOLM, M.D.(N.Z.), M.R.A.C.P.
From the Auckland Hospital

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The purpose of this article is to record a clinical and experimental study of muscle changes noted in a recent epidemic of poliomyelitis in New Zealand. The term muscle spasm has come into general use to describe those changes which occur in the acute stages of the disease and has to be distinguished from the state of contracture which is a terminal condition of muscle shortening due to fibrosis. In this study we are chiefly concerned with the state of muscle spasm encountered in acute poliomyelitis. The subject of muscle spasm has been a controversial one and skilled observers in the U.S.A. have stated that they encounter muscle spasm in all patients with poliomyelitis, whereas experienced neurologists and orthopaedic surgeons in the United Kingdom and the U.S.A. state that they have never encountered muscle spasm in the disease although, rather curiously, all agree that spasm occurs in the muscles of the neck and back, and in the hamstring muscles.

We regard muscle spasm in poliomyelitis as a state of shortening of muscle, encountered in the acute stage of the disease. Affected muscles are contracted and usually tender on palpation and on stretching; pain usually develops and the spasm increases. In some patients the spasm is not apparent in the muscles until stretch is applied.

Clinical Observations

Incidence of muscle spasm. At the outset of the epidemic attention was focused on the extensor muscles of the neck and spine and on the hamstring muscles, those muscles which in the past have been held to be affected by so-called 'meningeal irritation.' In our first 124 patients, evidence of muscle spasm in these muscle groups was detected in 89 per cent. Thereafter, it was realized that our method of examination for muscle spasm was inadequate and that a complete examination of a poliomyelitis patient, in addition to the usual examination of all systems, entailed a search for muscle spasm by a detailed inspection of all muscle groups, and further, big muscle groups should be taken through their full range of movement in order to observe the effect of stretch on the muscles. An examination of forty consecutive patients carried out in this manner revealed evidence of muscle spasm in 100 per cent.

TABLE I
INCIDENCE OF MUSCLE SPASM

	First 124 Cases		Last 40 Cases	
	No.	Percentage	No.	Percentage
Neck rigidity	90	73	25	63
Back rigidity	101	81	25	63
Kernig sign	96	77	18	45
Spasm of other muscle groups	Not fully examined	Not fully examined	25	63
Cases having one or other of above ..	110	89	40	100

Method of examination. This is best carried out in a warm room, with the patient clad in a pair of shorts and lying on a plinth, rather than on a bed. The patient is first inspected in the supine position for deviation of the head to the right or left or for undue extension of the head. The shoulders are examined for so-called 'cupping' in which there is updrawing and rotation forward of the shoulders, and the biceps for spasm which causes flexion at the elbows. Next the patient is inspected in the lumbar region for exaggeration of the normal lumbar lordosis or for scoliosis. On assuming the sitting posture, spasm and pain cause the patient to assume the 'tripod' posture with the knees and hips flexed, the lumbar region held straight and rigid and the body weight supported by the arms which are extended backwards (fig. 1). Before sitting up the legs should be carefully straightened out on the bed so that the internal malleoli are together. This may be difficult on account of spasm in the hamstring muscles. On sitting the patient up, one leg may shoot forward further than the other due to slight protective flexion at the hip on the affected side. The feet are inspected for inversion or eversion and for plantar flexion due

to spasm of the gastrocnemius muscle. The patient is then turned to the prone position in order to inspect the back muscles and the glutei muscles. After inspection in the above manner major muscles groups are stretched by taking them through their full range of movement. The trapezius muscle is tested by separating the head from each shoulder in turn. The usual test for neck rigidity is carried

FIG. 1.—Tripod position with muscle spasm of the lumbar and hamstring muscles.

out by slowly flexing the head. The muscles around the shoulder girdle are stretched by full abduction of the arm, and the biceps and triceps by full flexion and extension at the elbows. The lumbar muscles are stretched by lateral flexion to right and left and by asking the patient to touch the toes with the legs extended on the bed. Slight scoliosis of the spine may only be apparent when the patient stands and attempts to touch the toes, bending down and coming up slowly. The quadriceps may be stretched by full flexion by attempting to place the heel on the buttock or by turning the patient into the prone position and again attempting to put the heel on the buttock. The hamstring muscles are stretched by the usual Kernig test and the gastrocnemii muscles by dorsiflexion of the feet.

Manifestations of muscle spasm. Muscle spasm may be apparent when the patient is in a resting position. The affected muscles are usually tender on deep palpation and may be exquisitely so. To the touch they appear to be firmly contracted and the muscle tendons are tight. Stretching has the effect of increasing the muscle spasm in muscles already obviously in spasm and it may induce spasm in muscles which are apparently free of spasm. It is probable that the muscle spasm which is apparent at rest is brought about by stretch which is the result of postural change.

The effect of stretch is variable. In some patients muscles pass into painful spasm on the slightest stretch, and in others muscles can be taken almost to the end point of stretch before the patient complains of tightness and discomfort and spasm develops. The increase of spasm or the development of spasm on stretch usually occurs at the onset of a phase of painful stretch, but not invariably. It might be suggested that pain had set up an abnormally active stretch reflex. On the release of stretch to a point just short of pain the spasm passes off. If muscles are stretched beyond the onset of spasm resistance to further stretch increases. The degree of possible further stretch varies, and is limited at some times by extreme spasm and at other times by spasm and severe pain.

The sites of muscle spasm. The extensor muscles of the head and spine were those most commonly affected. In most patients the spasm of these muscles was apparent on stretch alone. In severe cases extension of the neck and back was apparent at rest and the knees were partially flexed. On occasions one side was more affected than the other, causing deviation of the head to one side, a tight ligamentum nuchae on one side or a scoliosis. When one lumbar group was more affected than the other there was flattening of the muscles on the affected side with a scoliosis with the concavity to the side of the flattened tight muscles. Muscles around the shoulder girdle were commonly affected causing the characteristic deformity referred to above. Spasm of the pectoral and latissimus dorsi muscles prevented complete abduction at the shoulder. The flexors of the forearm were sometimes affected and at times the pelvic girdle was tilted by spasm. In the thighs, the quadriceps muscles at times were partially or completely involved preventing complete flexion at the knee; when tested by flexion of the knee with the patient lying in the prone position, spasm and pain in the quadriceps muscle led to protective elevation of the buttock caused by flexion at the hip (fig. 2).

FIG. 2.—Spasm of quadriceps muscle with protective flexion at the hip on attempting to place the heel on the buttock.

Tightness of the gastrocnemius muscle was apparent on dorsiflexion of the foot, and, in some, spasm caused inversion or eversion of the foot. Spasm of the plantar muscles produced tightness and narrowing of the plantar fascia.

Other clinical features of muscle spasm. Aggravation of muscle spasm was caused by various activities, such as heavy massage or rough handling of muscles. Premature weight bearing with too early ambulation without adequate support (such as elbow crutches) also caused aggravation. On occasion patients were discharged from hospital apparently well, but after a time at home, as a result of unsuitable regulation of motor activity, muscle spasm developed again, at times necessitating further periods in hospital. For this reason, patients, when discharged, were advised to refrain from athletics, cycling, digging or other very strenuous activities for a few months, and for a time were examined regularly as out-patients. Exposure to cold caused aggravation in convalescent patients and sometimes was responsible for unmasking muscle spasm in mild cases which otherwise would not have been diagnosed as poliomyelitis. The effect of fever was apparent when an epidemic of influenza occurred. One girl, aged seventeen years, who had marked muscle spasm on admission, was almost symptom-free after six weeks. She then developed an attack of influenza (Type B. strain Lee), and with the onset of this intercurrent infection there was a prompt return of muscle spasm in the muscles previously affected. No change in the spinal fluid developed during this relapse. A similar reactivation of spasm was seen in some children who developed chickenpox and in some with mild upper respiratory infection.

No correlation was found between the degree of muscle spasm and the cell count of the spinal fluid. We encountered marked spasm in the presence of a normal spinal fluid and it was found to persist for weeks after the spinal fluid had returned to normal. During the epidemic many cases presented with a typical history of onset and characteristic muscle spasm without paresis or changes in the spinal fluid. Some muscles, apparently devoid of power, were found to be in a state of muscle spasm. This usually occurred as a result of reflex inhibition, due to fear of pain, and, on relief of the spasm and pain, power returned. At times weakness was the result of a disturbance of reciprocal innervation. The effect of effort in relation to the degree of paralysis has been noted by other observers. We have occasionally observed extreme aggravation of muscle spasm following strenuous exercise soon after the onset of the disease. One adult woman, two days after the onset of fever, danced for four hours and the following morning presented a picture of extreme spasm in many muscle groups, especially in the back and lower extremities.

The Relationship of Muscle Spasm to Paresis

The incidence of muscle spasm in the New Zealand epidemic was very high and occurred in 100 per cent. of cases fully examined. The incidence of paresis in the first 224 patients was 49·1 per cent. (110 patients).

Effect of treatment. Treatment of all patients in the acute stages of the disease was directed to the relief of muscle spasm and pain. Patients were nursed on a firm mattress which gave adequate splintage to the back muscles, and the feet rested against a foot board. The legs were prevented from rotating by sandbags and the weight of the bedclothes was taken by a cradle.

The relief of muscle spasm was accomplished by the use of hot packs made of a fine woollen material dipped in boiling water, wrung dry in an extractor, and applied at a high temperature. These packs were applied at hourly to four-hourly intervals during the day, and at night if required. This method of treatment relieved muscle spasm and produced a marked degree of comfort.

The ultimate state of muscles in spasm could not be predicted with certainty. The usual outcome was resolution of the muscle spasm without residual weakness or contracture. This resolution sometimes occurred within a few days; at other times it was delayed for many weeks. In some, the spasm passed into a state of permanent contracture due to fibrosis, which was an important factor in the production of deformities such as scoliosis. Some muscles in spasm passed into a state of partial or complete flaccid paralysis.

Electromyographic Studies

In an attempt to determine the site and nature of muscle spasm we made electromyographic studies on five normal patients and on twenty patients with poliomyelitis in various stages.

Method. The muscle action potentials were amplified by an all-mains operated amplifier. This was a resistance-capacity coupled amplifier, single ended, with a maximum gain which enables a 2 cm. oscillograph spot deflection to be obtained with an input signal of 100 microvolts. The amplified potential changes were led to two Cossor cathode ray oscillographs as well as to a loud speaker (Weddell *et al.*, 1944). It was therefore possible to view the action potentials on one oscillograph screen while these were being photographed on the other screen. As no screened room was available the amplifier was so constructed that the frequency response was substantially flat between 20 cycles and 2,000 cycles per second. All the records were obtained by the use of a concentric needle electrode in which the electrodes were threaded through a hypodermic needle so that the tips lay in the bevel of the needle (Adrion and Bronk, 1929). The action potential of a motor unit can give rise to a recordable impulse for a distance of the order of 1 cm. from the copper tip of the needle (Weddell *et al.*, 1944) and, in order to sample as large an extent of the muscle as possible, the needle was moved in several directions once the tip had penetrated the deep fascia and observations were made of the electrical potentials in each position. Thus the effects of physiological rest, of contraction, and of passive stretch were investigated.

Observations. The following observations were made (1) on normal muscles; (2) on muscles in spasm (a) at rest; (b) on passive stretch; and (c) on voluntary contraction.

NORMALS. In five normal subjects, on complete relaxation of the quadriceps muscle and on passive stretching of the muscle, no electrical potential changes were heard or seen but, on voluntary contraction, normal motor unit activity was demonstrated. The complexity of the tracing in respect of amplitude and frequency was dependent upon the force of the contraction.

(b) ON PASSIVE STRETCH. Each muscle was then submitted to a slow stretch to a point of discomfort or pain at which the muscle spasm developed, and in most cases action potentials developed. This, however, was not invariable. In a few cases, no potentials developed on stretch either with or without pain in spite of the development of spasm. In most cases, stretch was limited by maximum spasm and pain, in some by spasm alone, and at this point action potentials recorded were at a maximum.

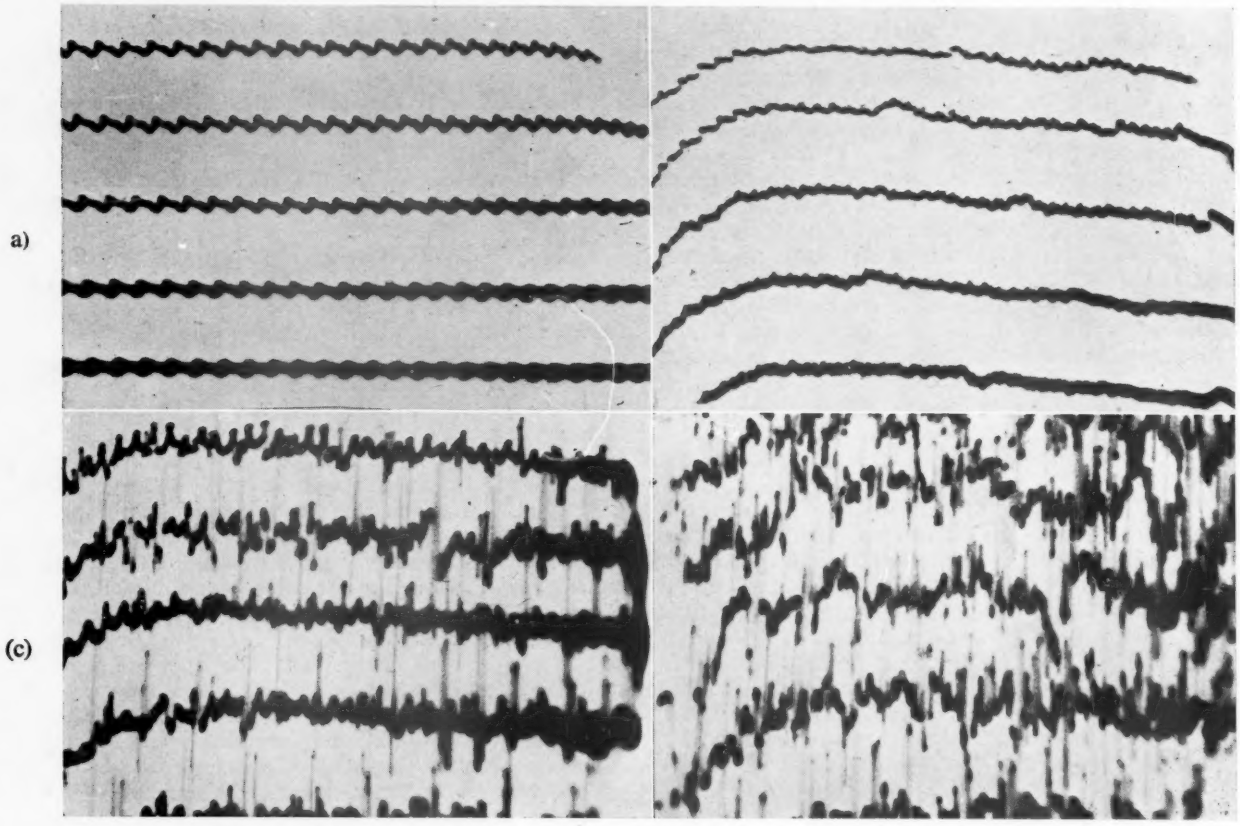

FIG. 3.—Electromyographs from patient with acute poliomyelitis with spasm of the right quadriceps muscle. (a) Muscle at rest; (b) effect of stretch which did not cause pain; (c) effect of painful stretch; (d) effect of voluntary contraction.

MUSCLES IN SPASM (a) AT REST. When the insertion action potentials had settled down, in most instances but not invariably, in a muscle which was clinically in a state of muscle spasm, there was electrical silence while the muscle was at rest. In some such muscles multiple sampling was carried out in order to confirm the result. In some muscles, fibrillation potentials were demonstrated, but in others which had had demonstrable spasm for more than three weeks, no fibrillation potentials were detected. We did not encounter spontaneous discharges from such muscles (figs. 3, 4, 5) as reported by Watkins *et al.* (1943).

These action potentials first appeared as the muscles entered the stage of painful stretch. In general, if some motor power was preserved, the action potentials on voluntary contraction were greater than those elicited on stretch. In some muscles, apparently paretic and in spasm, no action potentials could be elicited either on attempted voluntary contraction or on stretch, even to a point of severe pain. On slight relaxation, just to the point where pain ceased, the action potentials disappeared. We have not examined any muscle in which the unit

activity on stretch was greater than on full voluntary contraction as suggested by Watkins *et al.* (1943).

(c) ON VOLUNTARY CONTRACTION. In muscles in spasm capable of voluntary contraction, the frequency and amplitude of the action potentials obtained was in direct proportion to the degree of voluntary power present in the muscle.

Spinal Anaesthetic Studies

Kabat and Knapp (1944) tested five patients with spinal anaesthesia, three in the acute and subacute stage of the disease, and two in the chronic stage. Those in the acute and subacute stage showed relaxation of the muscle spasm under a spinal anaesthetic (heavy percaine). In two patients, fourteen months after the onset of the disease, spinal anaesthesia produced practically no change in the limitation of passive movement. Cook (quoted by Kabat and Knapp) in two patients in the first two weeks of the disease, found that spinal anaesthesia eliminated muscle spasm. In two patients under spinal anaesthesia, Kabat and Knapp found that when sensory anaesthesia was produced and some motor function still persisted, the restriction of passive movement was reduced but it was not completely eliminated until muscular paresis had developed.

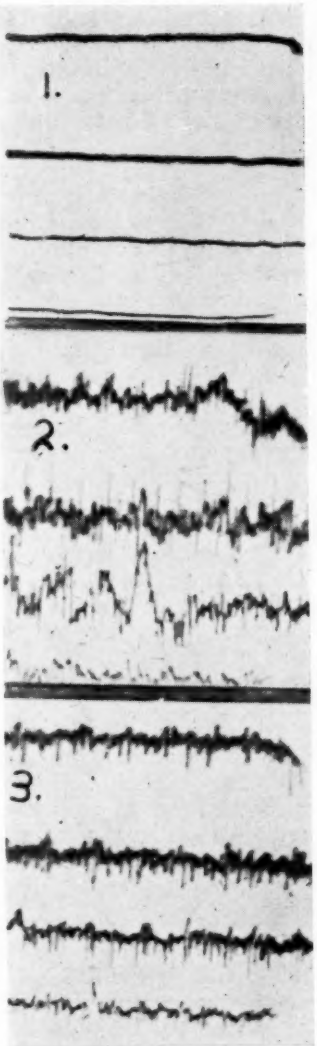

FIG. 4. Electromyographs of a muscle clinically showing spasm (1) at rest; (2) during maximum voluntary contraction; (3) during painful stretch of the muscle, demonstrating activity similar to motor unit action potentials.

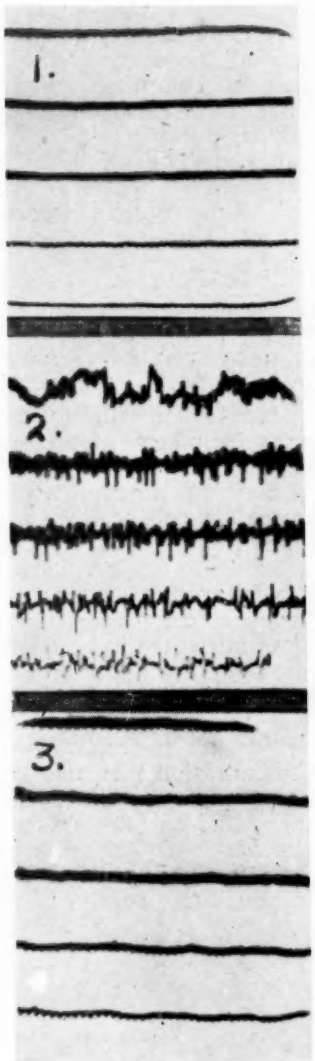

FIG. 5. Electromyographs of a muscle clinically showing spasm (1) at rest; (2) during maximum voluntary contraction; (3) during painful stretch of the muscle, demonstrating absence of activity.

We have studied the effect of spinal anaesthesia on four patients, two in the acute stage of the disease twenty and twenty-five days after the onset, and two in the chronic stage eighty-five and sixty-three days after the onset. Our yardstick was the goniometer, with which was measured the angle of flexion at the knee joint in checking the hamstring muscles and quadriceps muscles and the angle of flexion of the spine before and after spinal anaesthesia, using 2 ml. of heavy percaine. In the patients in the acute phase of the disease, spasm of the hamstrings, quadriceps, and back muscles was relieved. In the two patients in the chronic stage of the illness no relief was obtained. Hence, our observations conform to those of Kabat and Knapp and other observers (table 2).

Curare Studies

In this our experience was very limited but will be quoted. In two patients in the acute phase of the illness (sixteen and twenty days from the time of onset) curare (2 ml. 'intocostrin') failed to relieve muscle spasm. The curarized muscles were still painful on stretch. This small experience coincides with that of others (Kottke *et al.*, 1948; Elkins and Carbin, 1947) in respect of curare.

Discussion

Various authors have focused attention on the widespread nature of the lesions throughout the central nervous system. The main brunt of the lesion falls on the anterior horn cells of the spinal cord, on the internuncial cells of the cord and on the reticulum formation and tegmentum of the brain stem (Barnhart *et al.*). The changes in the meninges have received little attention. Scheinker (1947) has demonstrated changes in the leptomeninges similar to those in the cord. The meningeal infiltration varied considerably at different levels of the spinal cord and the cerebral meninges were affected only in the region of the mid-brain

and cerebellum. Freeman (1933) found infiltration of the meninges by lymphocytes at the base of the brain and particularly along the cord meninges. More recently changes in the muscles have been noted. Hassin (1943) has reported parenchymatous swelling and disruption of muscle fibres and also diffuse and focal inflammatory infiltration in a patient who died two hours after the onset of paralysis. Carey (1944) has studied muscles and their neuromuscular junctions, and has demonstrated in post-mortem material from three patients denervation of the extrafusal fibres within thirty-six hours of the onset of paralysis.

Older views on the normal mode of action of the spinal cord have to be revised in the light of recent work. We now have to visualize two opposing sets of impulses, excitatory and inhibitory, playing on the final common pathway, the anterior horn cell. In man, cortical suppressor bands have been proven in area 4 s. This suppressor system passes via the internal capsule to the caudate nucleus which relays to the red nucleus, substantia nigra, globus pallidus, subthalamic body, and the thalamus. From these nuclei, relays pass down the brain stem to the reticular nuclei, whence the band of suppressor bulbospinal fibres arise, pass to the internuncial pool, and thence to the final common pathway, the anterior horn cell. On available evidence it seems that the reticulospinal system constitutes an efferent pathway from the higher centres to the local spinal reflex system whose activity is expressed as suppression of anterior motor neurone discharge.

Various investigators have attempted to correlate exactly the known pathology with the state of spasm found on clinical examination, and have arrived at widely divergent opinions as to the site of the lesion responsible for the spasm, ranging from the reticulum in the bulbar region, the meninges, the internuncial cells, the anterior horn cells, to the muscle fibres themselves. Moldaver (1944) suggested that muscle spasm was made up of three components; meningeal irritation in the acute phase; increased stretch reflex due to paralysis of antagonists and hyper-irritability of inflamed posterior root ganglia. Kabat and Knapp (1944) have postulated damage of the internuncial neurones as the cause of spasm which results from release of proprioceptive reflexes from inhibition. Bodian (1946) has correlated injury to the bulbar inhibiting mechanism with the appearance of generalized spasticity in experimental poliomyelitis in monkeys, and Pohl (1943 and 1945) states that the present Kenny concept of the disease is that it is primarily an affection of peripheral structures, principally the muscles and their fascial coverings, but also including the skin and subcutaneous tissues.

Lesions of the suppressor system at different levels have been held to be responsible for muscle spasm as a result of the removal of inhibiting impulses and the resultant activation of the excitatory motor system. Relief of spasm by a spinal anaesthetic would support this view. On the other hand, a lesion of the suppressor system at the cortex, bulbar region or internuncial pool, would be expected to give rise to an upper motor neurone type of lesion with hyper-reflexia and a 'clasp knife' type of rigidity. We find, however, a different state from the hypertonus of the upper motor neurone lesion.

A consideration of our own findings suggests that more than one lesion accounts for the phenomena of muscle spasm.

Meningeal irritation. The available evidence lends some support to the theory of so-called 'meningeal irritation,' that is, reflex muscle spasm induced by irritation of pain-sensitive structures in the meninges or dorsal nerve roots such as occurs in meningitis or subarachnoid haemorrhage. By a series of studies Wolff (1947) demonstrates that noxious stimulation in any part of the cranium may lead to sustained contraction of the head and neck muscles. Pathological changes of the spinal fluid and meninges in poliomyelitis are well established and we believe that this inflammation causes irritation to the pain-sensitive structures and, as a result, reflex spasm of muscles of the neck, back,

TABLE 2

ANALYSIS OF DEGREES OF RELAXATION OBTAINED UNDER SPINAL ANAESTHESIA

Patient	No. of Days of Illness	Effect of Spinal Anaesthesia (Heavy Percaine)			Comment
		Before		After	
1	85	*Kernig (R)	145°	145°	No alteration
2	63	†Quadriceps (R)	30°	30°	No alteration
3	20	Quadriceps (R)	20°	0°	Definite relaxation
			30°	10°	
4	25	‡Back	65°	85°	Definite relaxation
		Kernig (R)	120°	150°	
		(L)	110°	155°	

* Kernig angles were measured as angle between leg and vertical thigh.

† Quadriceps angles were measured as angle between leg and thigh when heel was approximated to the buttock.

‡ Back angle was measured between horizontal plane of the bed and lumbar region when patient was leaning forward as far as possible.

and lower limbs. The release of spasm of the lower limbs by spinal anaesthesia in the acute phase of the disease would support this contention. There is, however, no apparent correlation between the number of cells in the spinal fluid and the degree of muscle spasm, as many cases have been shown to present with muscle spasm alone and a normal spinal fluid and, in the case quoted above, when muscle spasm was reactivated by fever, there was no evidence from the spinal fluid examination, as judged by the cell count, of a further meningeal lesion.

Peripheral lesion. The available evidence also lends some support to the suggestion of a peripheral lesion in the muscle itself, at the myoneural junction, or in the muscle protoplasm. Some pathological evidence has been quoted, and requires careful checking. Clinically the muscles are found to be tender on palpation and on stretch. The relief of the spasm by the application of hot packs might suggest a local lesion. It has been noted that at times the spasm is aggravated by motor activity, a febrile illness, or exposure to cold. These three factors normally induce muscle stiffness and all have the effect of increasing the metabolic rate with an increase of metabolites which may impair the chemical action at a damaged myoneural junction.

Electromyographic studies with our instrument failed to reveal motor potentials in spasm in spite of multiple sampling in some cases, and this suggests a primary involvement of the contractile mechanism of the muscle. The hyperirritability of the muscle on stretch suggests a sensitivity of the muscle spindles themselves. The relief of spasm in the acute phase by a spinal anaesthetic could be brought about by the abolition of pain or by the dilatation of blood vessels as probably occurs with the application of hot packs. The failure of curare to give relief favours the diagnosis of a lesion of the contractile tissue. Spasm may occur in muscles devoid of voluntary power and these muscles may go on to a flaccid paralysis suggesting that muscle spasm is not dependent upon the existence of an intact reflex arc. All these factors suggest that spasm in the acute phase is not entirely a function of the ordinary motor neurone.

Summary

We have found muscle spasm in all patients with poliomyelitis. It may be present at rest and is increased by stretch. It may resolve, or a muscle so affected may pass into a state of flaccid paralysis, or into a state of contracture.

Our electromyographic studies have failed to demonstrate electrical potentials in muscles in a state of spasm. We find increased sensitivity or hyperirritability of the stretch reflex.

Spinal anaesthesia relieved spasm in the acute stage of the illness but not in the chronic stage. Curare failed to relieve spasm in the acute stage of the illness.

In the acute phase of poliomyelitis, we believe the muscle spasm is in part the result of reflex spasm due to meningeal inflammatory changes irritating the pain-sensitive structures of the meninges and dorsal roots, and in part to a local lesion in the muscles themselves.

We have to thank Dr. Elizabeth Hughes who has given us access to her cases and has co-operated with us in this study; the N.Z. Medical Research Council for the release of the apparatus; Professor J. C. Eccles for his advice and assistance in this investigation. Mr. E. E. Suckling has given us technical advice, and Mr. Litherland has prepared the photographs.

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A SURVEY OF RECENT DEVELOPMENTS IN THE TREATMENT OF PNEUMOCOCCAL MENINGITIS

BY

W. P. U. JACKSON, M.A., M.D.(Cantab.), M.R.C.P., D.C.H.
From the Department of Clinical Medicine, University of Cape Town

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Doctors cure few diseases. When even an occasional patient begins to recover from a disease which previously carried 100% mortality, an impressive advance has been made, and when, later, such patients are actually expected to recover, then medicine may claim a triumph. This has happened with regard to pneumococcal meningitis.

Pneumococcal meningitis is not common, and no large series of cases have been described in Great Britain except those of Cairns and his co-workers at Oxford (Cairns *et al.*, 1944; Smith *et al.*, 1946). These particular reports were not fully representative of the general run of cases for at least two reasons; first, the great majority of these patients were adults, many being members of the armed forces, and secondly the treatment was carried out by a highly skilled team with the finest possible neurosurgical skill constantly at hand. For this reason, and bearing in mind that single cases are still being published, it was considered of interest to collect and analyse case records from different hospitals over the period of modern chemotherapy, tracing the changes in mortality rates as different agents were used, and then attempting to assess the present therapeutic value of penicillin and the most judicious method of its employment. For this purpose the records for the 11 years 1938-1948 of four large hospitals in Birmingham have been used. Several of the more recent cases have been seen personally. Before reviewing the Birmingham cases a short survey of the literature will usefully place them in perspective.

The Pre-Chemotherapeutic Era

Goldstein and Goldstein found 150 recoveries reported in the literature up to 1927, and Steele and Gottlieb (1941) found a further 30 between 1927 and 1939. (Incidentally horse antiserum was introduced in 1930, but was evidently not very effective.) Two large single series with 100% mortality rates were those of Toomey and Roach (1939) from Ohio (159 cases), and of Silverthorne (1948) from Canada (121 cases).

The majority of recoveries reported seem to have been in those cases which were secondary to ear disease, and perhaps the primary condition had really produced a local arachnoiditis rather than a more general leptomeningitis in these patients. Certainly some such explanation must be suggested for the remarkable report of Adam and Connal (1937) of seven recoveries from nine cases, especially since their radical treatment of the otitic state itself, as soon as meningitis was suspected, was so successful. Allman (1937) published an account of another recovery in an otitic case in the same year.

TABLE 1
RESULTS OF CHEMOTHERAPY IN THE LATER SULPHONAMIDE ERA

Author	No. of Cases	Recoveries (%)	Remarks
Better Results			
Rhoads *et al.* (U.S.A., 1940)	22	32	
Hodes *et al.* (U.S.A., 1943)	60	42	
Appelbaum (U.S.A., 1945)	139	35	
Jaffe (South Africa, 1946)	24	41	
Walker and James (U.S.A., 1945)	5	4	Radical surgical treatment of primary focus
Poorer Results			
Sweet *et al.* (U.S.A., 1945)	40	7·5	
Dowling *et al.* (U.S.A., 1942)	72	5·5	Pooled cases
Silverthorne (Canada, 1948)	47	14	
Present series (Birmingham)	82	20	Pooled cases

TABLE 2

ANALYSIS OF REPORTS OF RECOVERIES USING PENICILLIN AND SULPHONAMIDES

	Cases	Recoveries (%)	Penicillin (Dosage and Route)	Sulphonamide	
Waring and Smith (U.S.A.), 1944 ..	21	33	5–20,000 units intrathecally daily, also intramuscularly	Nil	
Waring and Smith (U.S.A.), 1944 ..	12	92	5–20,000 units intrathecally daily, also intramuscularly	Adequate	
Cairns *et al.* (Oxford), 1944	19	63	Intrathecally and intramuscularly	Nil	
Cairns *et al.* (Oxford), 1946	19	88	Intrathecally and intramuscularly	Adequate	100% recovery in 13 fully treated cases
Appelbaum and Nelson (U.S.A.), 1945	67	39	5–20,000 units intrathecally daily + intramuscular or intravenous injections also	Discontinued early	
Sweet *et al.* (U.S.A.), 1945	16	44	Intrathecally and intramuscularly	Variable	
White *et al.* (U.S.A.), 1945	50	36	No intrathecal drug in seven cases. Dosage variable	Variable	From several centres (pooled)
Hutchins and Davis (U.S.A.), 1945 ..	14	4 full recoveries, 5 with residual C.N.S. damage	Intrathecally and intramuscularly	Adequate	All under 2 years of age
Hall *et al.* (U.S.A.), 1946	17	76	10,000 units intrathecally b.d., also intramuscularly	Adequate	
Hall *et al.* (U.S.A.), 1946	162	45·7	Various	Various	Review of all reports up to 1946
Ross and Burke (U.S.A.), 1946 ..	19	88	5,000 units intrathecally b.d. + intramuscular or intravenous injections also	Adequate	
Klepacki (Poland), 1947	3	0	Intrathecally and intramuscularly	Nil	All children
Klepacki (Poland), 1947	5	3	Intrathecally and intramuscularly	Given	All children
Peittsara (Finland), 1947	10	60	Intrathecally and intramuscularly	Given	

The Early Sulphonamide Era

In June, 1937, Mertins and Mertins recorded the recovery of an otitic case on prontosil, and in the same month Caldwell and Byrne described the cure of a non-otitic patient, but unfortunately pneumococci were not actually isolated on culture. In 1938 Finland *et al.* reported six recoveries in ten cases treated with sulphanilamide combined with frequent complete cerebrospinal fluid drainages and specific rabbit antiserum given intrathecally. Reid and Dyke (1938) were the first to claim recovery after the use of sulphapyridine. By 1939 more than 30 cures had been reported (Hewell and Mitchell). Raman (1939) claimed to have cured the first case after a true single relapse, using sulphapyridine.

There was, as usual, a tendency to report only good results, and Steele and Gottlieb in 1941 found 115 cases in the literature treated with sulphanilamide or sulphapyridine with a 66·6% recovery rate. In this collection the results with sulphanilamide were slightly better than those with sulphapyridine. Antiserum given in addition was found to be valueless. No recovery had been described under the age of two years. Of the larger series, MacKeith and Oppenheimer (1939), Neal *et al.* (1940), and Leyshon (1942) reported a high proportion of recoveries (45% in 47 cases). In the present series from Birmingham there were no recoveries in the 17 cases treated with sulphanilamide only.

The Later Sulphonamide Era

A whole spate of papers now appeared reporting very variable results of treatment. A few quotations will suffice.

It is noteworthy that two series from the poorer result group were pooled from various hospitals. Thus Dowling's 72 cases were the total number notified in the city of Washington between January, 1938, and December, 1942. This series includes cases treated by all types of sulphonamide.

The Penicillin Era

Reported cases and series now become extremely difficult to analyse because of differences in the dosage, purity, and route of injected penicillin, and because of the variable combination of sulphonamides with it. These new distinctions between different accounts, and even within single series, added to the existing variabilities (e.g. age of patients; pooled, single-hospital or single-team series; dosage and type of sulphonamide) render doubtful the value of comparisons. Moreover the importance of several reports is greatly diminished by the complete omission of any statement regarding these factors as they apply to any particular series.

Barker in December, 1943, published the first account of a recovery after the use of penicillin, and at almost the same time Keefer *et al.* (1943) reported 23 cases with seven recoveries, but their dosage was small and the intrathecal route was frequently not used. Other reports may be compared in tabular form (Table 2).

It must be admitted that some of these results are no better than those reported by Appelbaum (1945) and by Hodes, Smith, and Ickes (1943) using sulphonamides only. However, a truer picture of the value of modern treatment is obtained by considering together those series in which more or less full and adequate therapy was given. Taking cases which received 5,000-40,000 units of penicillin intrathecally at least daily for not less than five days, together with adequate sulphonamide dosage, it is found that a recovery rate of 79% is recorded in 101 patients. This figure would probably be improved further if patients who died within a few hours of admission to hospital were excluded.

Present Series

The quotations in Table 2 demonstrate the value of continuing sulphonamides with penicillin, the superiority of this combined therapy being evident throughout.

Table 3 calls for little comment. If only those cases which were adequately treated with penicillin and sulphonamides and did not die within 48 hours of admission are considered separately, there are 24 cases with 17 recoveries (72%).

Table 4 accentuates the poorer prognosis in young

TABLE 3

ANALYSIS OF TREATMENT IN PRESENT SERIES

Treatment	Total No. of Cases	Recoveries	Recovery (%)
Nil specific	13	0	0
Sulphanilamide	17	0	0
Sulphapyridine and sulphathiazole	73	14	10·7
Later sulphonamides	9	3	
Penicillin (less than 10,000 units per day intrathecally with intramuscular penicillin and sulphanilamide)	8	4	
Penicillin (as above, but more than 10,000 units per day intrathecally)	33	22	67
Incomplete (e.g. penicillin without sulphonamide)	10	3	30
All cases	163	46	29

TABLE 4
PROGNOSIS RELATED TO AGE

Age (in years)	Total No. of Cases	Recoveries	Recovery (%)
Under ½	23	2 (both treated with penicillin)	8·7
½–2	45	12	27
2–12	48	18	38
12–40	13	6	46
Over 40	34	8	24

infants, a feature also noted during the sulphonamide era by Hodes *et al.* (1943), Alexander (1943), and Jaffe (1946). Steele and Gottlieb (1941) remarked that, despite 66·6% recoveries in 115 reported cases in the earlier sulphonamide days, all cases under 2 years of age had died. Indeed, recoveries in infants before the use of penicillin were rare, although Jacobsen (1945) reported a baby of 3 months cured with sulphapyridine, and another of 14 months, out of a total of 14 patients. The use of penicillin has so greatly improved the prognosis in the infant that White *et al.* (1945) thought it no different from that of the adult, and Ross and Burke (1946) reported a series of nine cases under the age of one year, all of whom recovered. Nevertheless such results cannot be claimed by all (Waring and Smith, 1944; Hutchins and Davis, 1945; Klepacki, 1947).

There were also a few cases of peritonitis (3), empyema (2), endocarditis (2), bronchitis (1), and meningocoele (1).

These figures bear out the suggestion of Hodes, Smith and Ickes (1943) that meningitis secondary to a pneumonia carries a worse prognosis, but White *et al.* (1945) on the other hand consider that a primary focus in the head is worse than a pulmonary one.

No serious cerebral sequelae were recorded, unlike those in the series of Hutchins and Davis (1945), and Jaffe (1946). Spinal block during intrathecal penicillin therapy was suspected only once, and this was doubtful. Neither cerebral abscess, cauda equina damage, nor residual mental defect was noted.

One curious feature was the occurrence of unilateral orbital oedema of quite gross degree in three cases, two seen personally. The swelling came on in each case a day or two after the onset of the meningitis, and was not combined with any proptosis. In one case (Case 8) it was accompanied by complete third nerve palsy of that side. There were no fundal changes. The oedema cleared up within ten days in all cases. In view of the frequency with which cerebral venous thromboses are found at necropsy in cases of pneumococcal meningitis, it seems likely that this orbital oedema was caused by thrombosis of an orbital vein.

Deaths Despite Apparently Full and Adequate Treatment

Cairns and his co-workers (Smith *et al.*, 1946) consider that there is no reason why the general mortality rate for pneumococcal meningitis should not be as low as 10%, which figure they succeeded in reaching in their own later series. Among the present cases there appear to have been 24 who were fully treated with intrathecal and systemic penicillin and sulphonamides on the lines advocated by Cairns, and on whom the greatest care was expended. None who died within 48 hours of admission are included. Nevertheless seven succumbed.

Case Reports

Case 1. Aged 12 months. Complicated by diarrhoea. Died two days after admission. Gross hepatic damage evident at necropsy.

Case 2. Aged 4 months. Meningitis was a complication of pneumococcal peritonitis. The C.S.F. could not be completely cleared of the organism, which persisted despite raising of the intrathecal dosage to 100,000 units daily. Death after 30 days' treatment in status epilepticus. No C.S.F. block. No evident reason for lack of response was found at necropsy. Was the epilepsy due to the disease or to the (pure) penicillin ?

Case 3. Aged 13 months. Child developed left hemiplegia, choreiform movements, and recurrent fits. The C.S.F. remained sterile for 11 days before death. No hydrocephalus was found, but presumably severe functional brain damage had been caused.

TABLE 5
APPARENT PRIMARY CONDITIONS

	None	Middle-Ear Disease	Pneumonia	Tonsillitis	Sinusitis
Total No.	47	36	33	6	3
Recovery rate (%)	39	50	18	50	0

TABLE 6
COMPLICATIONS RECORDED

	No. of Cases	Remarks
Convulsions	37	(See below)
Squint	14	Cleared entirely in patients who recovered
Hemiplegia	9	
Endocarditis	4	All died
Nystagmus	3	
Unilateral orbital oedema	3	? cause
Pericarditis	2	Both died
Purpura	1	
Deafness (total)	1	The only permanent residuum recorded
Total No. of Cases	163	

Case 4. Aged 6 weeks. There were at least seven days before treatment was started and a grossly bulging fontanelle presented on admission. Lateral and superior sagittal sinus thromboses were found at necropsy.

Case 5. Aged 2 years. No apparent response whatever. Death after two days' treatment, with terminal convulsions. Dosage of intrathecal penicillin was 40,000 units of the pure salt. No reason was found for lack of effect on the C.S.F.

Case 6. Aged 48. Left lower lobar pneumonia was the primary condition. Death after three days, with no apparent reason for failure of sterilization of the C.S.F.

Case 7. A boy aged 17 months was admitted to hospital with a diagnosis of right mid and lower pneumonia (W.B.C., 33,000). Treatment was begun with intramuscular penicillin, 25,000 units three-hourly, and sulphamezathine, 1 g. and 0·5 g. four-hourly. Progress was excellent until nine days after admission when neck rigidity was noticed, without fever or apparent illness, and pneumococci were isolated from the C.S.F. Treatment was continued as before, but in addition intrathecal pure penicillin (25,000 units) followed by 10,000 units daily was given. The C.S.F. rapidly cleared, but 16 days after admission organisms reappeared in the C.S.F., with rapid clearance again. Twenty days after admission the child was worse, and had right sided convulsions with remaining right hemiplegia.

Twenty-six days after admission the child was again worse, with vomiting and further fits, and serous discharge from the right ear. Organisms were again found in the C.S.F. The baby was transferred to the neurosurgical department, where ventriculography was performed but no block or abscess was discovered. Culture was positive (cells 1,044). Intraventricular pure penicillin (20,000 units daily) was given.

Twenty-seven days after admission the ventricular fluid was sterile. On the succeeding days the fluid rapidly cleared and cells dropped to 40, but generalized convulsions and even status epilepticus continued to occur for some days. There was an occasional mucopurulent discharge from a posterior perforation in the right ear, but no radical treatment seemed indicated.

Forty-seven days after admission there was a rise of temperature for no apparent reason, which settled after seven days.

Seventy-five days after admission there was a rise of temperature again, and 77 days after admission the child died in coma, without any explosive episodes.

Necropsy revealed pus in both middle-ear cavities and a sterile exudate around the base of the brain and brain-stem, with no other evident reasons for death.

The cause of failure in all these cases except No. 1 is not obvious, but is evidently various. In none was there the slightest evidence of C.S.F. blockage, and only in Case 4 can it be said that there was undue delay before the start of therapy, whereas in Case 7 the meningitis actually developed under the eye of the physicians and was promptly treated. No penicillin-insensitive organisms were ever isolated. It would seem that the finest present day treatment cannot be guaranteed to sterilize the C.S.F. even in uncomplicated cases, and even if the C.S.F. is cleared residual intracranial damage may sometimes progress to death.

Therapeutic Considerations

The present standard method of treatment using intrathecal penicillin, with its attendant dangers and difficulties, is fully described by Cairns (Smith *et al.*, 1946), so that the intention in this article is merely to consider one or two particular points.

By ' standard ' treatment is meant the injection of pure penicillin intrathecally, 10,000-20,000 units 12-hourly initially, and then once daily; penicillin intramuscularly, about 1,000,000 units daily in divided doses; and a sulphonamide given in full doses, say, 1 g. per stone per day for an adult. This treatment should be continued for at least a week after the C.S.F. is sterile.

Dosage of Intrathecal Penicillin. Single doses of 40,000 units and over have often been found to produce toxic reactions (Cairns *et al.*, 1944; Sweet *et al.*, 1945; Walker, 1947) and these have included

arachnoiditis, myelitis, paraplegia, cauda equina damage, pain and weakness in the upper limbs, and convulsions. On the other hand Reuling and Cramer (1947) used 50,000 units repeatedly and never saw any damage result. Reitz (1946) gave 100,000 units 12-hourly to one case without any deleterious reaction. Neymann (1945) found 40,000 units of 40% purity satisfactory in general paralysis of the insane, and recent accounts of influenzal meningitis have included this range of dosage (Gerrard, 1947; Gottlieb *et al.*, 1947). In the present series doses of 50,000 units and over (in two cases a few repeated doses of 200,000 units) were often used without any ill effects. Under 20,000 units a day is probably too little, and there are some patients who seem to need considerably more (see Case 8). Certainly this may be given in divided doses 12-hourly, but with the now generally used pure crystalline G salt a large intrathecal dose can be tolerated, and indeed no reports have been found of toxic reaction to any dosage of the pure salt, either clinically or experimentally. The use of intrathecal penicillin has not increased the incidence of convulsions in pneumococcal meningitis, but rather the reverse, as the figures from the present series suggest:

In 107 pre-penicillin cases, fits were recorded in 29 (27%).

In 56 penicillin-treated cases, fits were recorded in 8 (14%).

The following case (Case 8) is an interesting illustration of some of the preceding points.

Case 8. A boy aged 18 months was admitted to hospital, having been ill for two days and showing signs of right apical pneumonia. The neck was rigid, but lumbar puncture revealed a clear C.S.F. He was treated with sulphamezathine. Two days after admission there was complete right third nerve palsy and gross right orbital oedema. The C.S.F. was now turbid, and pneumococci were found on smear and culture. Pure penicillin, 20,000-50,000 units daily intrathecally, at first in divided and later in single doses, was given, together with 20,000 units intramuscularly four-hourly, and sulphamezathine 0·7 g. four-hourly. The C.S.F. was sterile after 48 hours. Six days after admission the baby was much improved in every way, and the C.S.F. was still sterile. A blood count showed a leucopenia (under 1,000 polymorphs). The sulphamezathine dosage was reduced to 0·4 g. four-hourly.

The white count rose steadily in succeeding days, despite continuation of sulphonamide.

Eleven days after admission the intrathecal penicillin and sulphamezathine were discontinued, but 13 days after admission there was a recurrence of symptoms and of bacteria in the C.S.F. on smear and culture, and the full therapy was resumed.

Twenty-three days after admission the baby had developed a sero-purulent discharge from the right ear, but surgery was not indicated. Twenty-seven days after admission the child seemed well, and again the intrathecal penicillin and sulphamezathine was discontinued.

However, 28 days after admission there was a second clinical and bacteriological relapse, and full therapy was resumed.

After this there was consistent clinical improvement, no further rise of temperature, and complete recovery of the third nerve palsy, despite three further bacterial relapses during the next three weeks. These relapses were accompanied by a consistent fall in the protein level and in cells in the C.S.F., although intrathecal penicillin was continued in high dosage. In two relapses the cocci were grown in culture, but in the third they were seen only on the smear.

Treatment was continued (with breaks only as indicated above) for eight weeks, and the residual penicillin in the C.S.F. was estimated daily. The persistence of penicillin was found to be extremely variable. No trace was ever found after less than 50,000 units given during the preceding 24 hours and on this dosage the residual drug varied from 0 to 7 units per ml. Even when given 12-hourly at least 25,000 units were needed to produce any persistence at the time of the next injection. This case also indicates the importance of long-continued, intensive therapy.

Are Intrathecal Injections Necessary? Despite the contention of Rosenberg and Sylvester (1944) that 24-40,000 units of penicillin administered intramuscularly or intravenously were sufficient to produce reasonable penetration into the C.S.F. in meningitic cases, the consensus of opinion has been that intrathecal therapy is necessary in pneumococcal meningitis (Rammelkamp and Keefer, 1943; Cairns and Smith *et al.*, 1944, 1946; Anderson, 1945; Smith, 1945; Ross and Burke, 1946). More recently, however, Lowrey and Quilligan (1948) reported 14 recoveries out of 17 cases without intrathecal penicillin. All the last seven cases recovered. These received 100,000 units intravenously repeated twice and followed by 400,000 units daily intramuscularly, together with sulphadiazine in doses of 1·5 g. per stone bodyweight per day. Dowling *et al.* (1949a) treated 21 cases with doses of 1,000,000 units intramuscularly two-hourly and found 0·08-1·25 units per ml. in the C.S.F. after eight hours. Only two cases died after being treated more than 24 hours. The authors were encouraged to give such large doses by the report of Schwemlein *et al.* (1946), who showed that penicillin penetrated into the C.S.F. in therapeutic quantities in 100% of people who received 20,000,000 units in 24 hours, and also by their own series of 16 cases in which intrathecal penicillin was used with only seven recoveries. Dowling and his co-workers in a further report (1949b), remarked on a more rapid fall in temperature and in pleocytosis in the C.S.F. using intramuscular therapy only. Sulphonamides were found to be unnecessary. Other authorities commenting on this report (Spink, 1949; Boger, 1949) agreed that penicillin given in this way appeared completely

adequate. It would seem, then, that this method of therapy should be more widely tried, since it obviates the difficulties and dangers of multiple intrathecal injections and may, perhaps, produce even better results. Incidentally Duthie (1944) showed that 1/40 unit of penicillin per ml. was usually lethal for the pneumococcus, and there is no evidence that penicillin resistance ever develops in a case under treatment. It must be pointed out that the value of this type of therapy in infants has not yet been assessed.

Are Pneumococci in C.S.F. Always Pathogenic? Occasionally it was observed that a bacterial relapse in the C.S.F. was unaccompanied by concomitant clinical signs, and that the patient's recovery was, in fact, quite unimpeded despite the renewed presence of pneumococci. In these circumstances there was no accompanying rise in cells, nor in protein levels, nor any fall in chloride or sugar levels in the C.S.F., and in fact the improvement in these findings continued uninterruptedly. Patient No. 8 is an example. During his last relapses the cells in the C.S.F. were below 10 per c.mm. It is suggested therefore that in certain bacterial relapses the pneumococci are actually non-pathogenic and their finding then is evidence of a symptomless infection, partially comparable with some *Bact. coli* bacillurias, or with the excretion of typhoid bacilli from a carrier's gall bladder.

This suggestion has also been made by Traut (1945), who reported an interesting case in which pneumococci recurred in the C.S.F. for several months at approximately monthly intervals. I did not know of Traut's case when this idea occurred to me.

The Special Problem of the Young Infant

Recovery in infants was extremely uncommon before the advent of penicillin. Now, however, some of the poor results are undoubtedly related to difficulty and delay in the diagnosis of meningeal disease. Since such excellent results have been obtained by some physicians (White *et al.*, 1945; Ross and Burke, 1946; Alexander, 1947) an awareness of the difficulties of early diagnosis in the infant is evidently of great importance. Metcalfe (1948) has reported a recovery in an infant who was eight days old when the meningitis was diagnosed, but who was in hospital at the time and was promptly treated.

Alexander and Ellis (1942) and Alexander in 1943, commenting on the diagnostic difficulties in infants under seven months, drew attention to the importance of a slight increase in tension of the fontanelle, alternating drowsiness and irritability, a high pitched cry, and a vacant look in the eyes, especially when any of these are combined with fever. Hogg and Bradley (1945) remark that the presenting symptom may be vomiting, diarrhoea, irritability, otitis media, or pyrexia of unknown cause, while the occurrence

TABLE 7

SURVEY OF CLINICAL FEATURES OF TWENTY CASES

Case	Age	Result	Outstanding Features
1	6 days	Death	Fever, refused breast, squeaky cry, full fontanelle. Fits at onset.
2	8 days	,,	Two months premature. Jaundiced. Pneumonia present. Otitis media and meningitis revealed at necropsy.
3	4 weeks	,,	Two fits recorded. Otitis and meningitis revealed at autopsy.
4	4 weeks	,,	Gastro-enteritis. Convulsions.
5	6 weeks	,,	Otitis media and signs of meningeal irritation.
6	6 weeks	,,	Tense fontanelle.
7	8 weeks	,,	Otitis media. Fits at onset. Vomiting, fever, depressed fontanelle. Not diagnosed in life.
8	8 weeks	,,	Fever (pyrexia of unknown origin). Not diagnosed.
9	10 weeks	,,	Gastro-enteritis, otitis media, thrush oesophagitis, and bronchopneumonia. Meningitis found at necropsy.
10	10 weeks	,,	Cough with wheezing. Good weight gain. Irritability and occasional vomiting developed later, but the diagnosis was not suspected until twitching of right arm and leg started.
11	3 months	,,	Mastoiditis. Fits.
12	3 months	,,	Pneumonia. Convulsions at onset, fever, vomiting, excessive crying.
13	4 months	,,	Initial fits, squint, and seventh nerve palsy.
14	5 months	Recovered	Status epilepticus and paroxysmal tachycardia.
15	5 months	Death	Otitis media, fits.
16	5 months	,,	Convulsions.
17	5 months	Recovered	Otitis media. Vomiting and drowsiness. Passed into coma with cyanosis and hemiplegia.
18	6 months	Death	Bronchopneumonia. Fits.
19	6 months	,,	Otitis media. Squint and fits.
20	6 months	,,	Otitis media, fever, macular rash. No irritability, fits or meningism. Not diagnosed in life.

of convulsions with any of these strongly suggests meningeal involvement. Even in pre-chemotherapeutic days the difficulties in making this diagnosis were pointed out by Koplik (1916) and Cooperstock (1938).

Twenty case records of patients under seven months of age in the present series have been surveyed, in the hope of helping to assess which clinical features might be of the greatest value as diagnostic pointers. They are summarized in Table 7.

Of these 20 cases diagnosis was made only at necropsy in six, and was too late in several others to be of any value. It is noteworthy that 13 had convulsions, mostly at the onset of the disease. Eight cases showed neither signs of meningeal irritation nor tenseness of the fontanelle. In fact the limb signs of meningitis (Kernig, Brudzinski) appeared quite valueless. Stiffness of the neck, a sign of greater importance, is difficult to assess in the infant. When present it may be noticed that the baby prefers to lie on his side rather than on his back, so as to allow slight retraction of the head to occur even when the neck is not markedly stiff. The best test for minor degree of neck rigidity is gently lifting the head with the flat hand behind the occiput of a quiet infant, when, in a normal baby who is not crying, the chin immediately collapses on to the chest.

Middle-ear disease accompanied the meningitis in ten cases, pneumonia in three, and gastro-enteritis in two.

It would seem that meningitis should be suspected and lumbar puncture performed in the following circumstances, even in the absence of any confirmatory signs.

(1) Otitis media with fever which does not immediately respond to therapy.
(2) Vomiting not due to obvious cause, especially if accompanied by fever.
(3) Unusual drowsiness and lack of interest in food.
(4) Change in type of cry; excessive crying and irritability.
(5) Convulsions occurring for the first time, even if with no other symptoms.
(6) Tense fontanelle.
(7) The development of paralytic phenomena, e.g. squint.

Particularly dangerous is the tendency to consider fits to be the natural concomitants of teething, otitis, pneumonia, feeding disturbance, etc. Intracranial disease should always be suspected.

Therapy in young infants is usually on the same lines as in older people, but Alexander (1947) has claimed improved results from the addition of intravenous specific rabbit antiserum. She had six recoveries in eight infants under six months old using her serum together with standard penicillin and sulphonamide treatment.

Summary

An attempt has been made to trace the development of the recent therapy of pneumococcal meningitis and to note its effect in progressively lowering the mortality rate of this disease. A series of 163 cases occurring in Birmingham during the last 11 years has been analysed. It is evident that the prognosis of pneumococcal meningitis in general is not as good as we might expect, although the causes of failure in therapy are not always obvious.

The special problem of diagnosis in the infant has been considered, since the signs of meningeal infection at this age are usually atypical and frequently misinterpreted. Recent trends in the methods of using penicillin are discussed, and it seems possible that very large doses of this drug given intramuscularly may obviate the necessity for intrathecal injections and the use of sulphonamide.

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PROTEIN REQUIREMENTS OF INFANTS

3. THE NUTRITION OF PREMATURE INFANTS*

BY

W. F. YOUNG, M.D., D.C.H., P. POYNER-WALL, M.B., B.S., D.C.H.,
H. C. HUMPHREYS, M.B., B.Chir., D.C.H., E. FINCH, M.Sc.,
and I. BROADBENT, M.A.

From the Children's Hospital and Department of Paediatrics and Child Health, University of Birmingham

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During the first year of life the mortality rate is higher for prematurely born infants than for those born at term. In a recent study by Crosse and Hallum (1947) it was found that even after the first month of life, the mortality was 47 per 1,000 premature live births (twice as high as for full-term infants), infection being the main cause of death. There are no statistics for the morbidity rate, but this must also be high. Premature infants are known to become anaemic (Parsons and Hawksley, 1933; Mackay, 1935; Blackfan, Diamond, and Leister, 1944), and it seems probable that this and other effects of nutritional deficiency may contribute to the high death rate from infection. It is important therefore to supply premature babies with their full requirements for optimum nutrition and to continue to do this for some months after their discharge from hospital.

Nitrogen and Protein Retention in the Foetus and Full-term Infant

Knowledge of growth and nitrogen retention in the foetus during the later weeks of gestation may be used to outline a pattern of the needs of the premature baby. One of the most serious handicaps of premature birth is the low content of protein and of minerals in the body. Premature infants born after the twenty-eighth week are sometimes viable, but most of those who survive are born after the thirty-second week of gestation and then weigh about 1,500 g. The development of the foetus of this age and weight whose gestation is continued to term compared with that of the full-term infant during the first month of life is shown in Table 1. During the ninth and tenth lunar months the foetus gains about 690 g. and 1,000 g. respectively of which 100 g. and 155 g. are protein (Macy and Hunscher, 1934 ; Huggett, 1946). On a basis of bodyweight this is about 2·0 g./kg./day, whereas the full-term infant during the first month of life retains 1·0 g./kg./day of protein (Beach, Bernstein, and Macy, 1941), and as it grows older the amount falls to about 0·75 g./kg./day (Daniels and Hejinian, 1929; Jeans and Stearns, 1933; Nelson, 1930; Albanese, 1947). If the premature infant is to follow the pattern of growth which it would have achieved *in utero*, it must continue to retain as large amounts of protein as would have been laid down if gestation had been continued to term.

Utilization of Protein by Premature and Full-term Infants

Gordon, Levine, Wheatley, and Marples (1937) found that premature infants fed on human milk (or 'humanized' cow's milk mixtures) utilized about 70% of protein, retaining an average of 0·245 g. of nitrogen which is equivalent to about 1·5 g. protein/kg./day and represents a highly efficient use of the food. Full-term infants fed on similar diets retain less nitrogen, their utilization of protein being of the order of 50% which is equivalent to about 1 g./kg./day (Beach *et al.*, 1941). By raising the quantity of cows' milk—and hence the protein—given to full-term infants, Nelson (1930) found that increased amounts of nitrogen were stored and that the babies gained more weight, but the maximum retention of protein was only about 1·3 g./kg./day and not nearly as great as that which is laid down by premature babies on high protein diets. Thus nitrogen balance studies in premature infants aged 6-60 days (Gordon *et al.*, 1937) showed that more nitrogen was retained as the protein intake was increased from about 2·8 to 5 g./kg./day, and, with the larger amounts,

* Part of a report prepared for the Medical Research Council's Committee on the Protein Requirements of Infants.

TABLE 1

A. GAIN IN WEIGHT AND PROTEIN RETENTION OF FOETUS IN LAST TWO MONTHS OF GESTATION AND INFANT IN FIRST MONTH AFTER BIRTH AT TERM. B. PROTEIN REQUIREMENTS OF PREMATURE AND FULL-TERM INFANTS BASED ON 'THEORETICAL' NEEDS AND UTILIZATION OF PROTEIN

		Foetus in Utero		Full-Term Infant
		Ninth Lunar Month	Tenth Lunar Month	First Month of Life
A.		g.	g.	g.
Gain in Weight (g.)	per month	690	1,000	750
	per day	25	36	27
	per kg. bodyweight per day	13·5	13·2	7·1
Retention of Protein	per month	100	155	110
	per day	3·6	5·5	3·9
	per kg. bodyweight per day	2·0	2·1	1·0
B.		Premature Infant		Full-Term Infant
Protein required by Infants	per day	7·2+	11·0+	11·0
	per kg. bodyweight per day	4·0	4·0+	about 2·0
Gestational Age in Weeks		32	36	Term 40

the average retention was 0·352 g. nitrogen, which is equivalent to about 2·2 g. protein/kg./day, i.e. about 50% utilization. It therefore seems probable that the diet of premature infants should contain at least 4 g. of protein/kg./day in order to allow retention of about 2·0 g./kg./day during the period corresponding to the thirty-second to fortieth weeks of gestation (see Table 1). Levine and Gordon (1942) have used 6·0 g./kg./day and it may be advantageous to give these large amounts to provide for a specific need for individual amino acids. Human milk and modified cow's milk formulae with a protein content based on that of human milk may not supply enough protein. Thus 150-180 ml., the usual volume to be well tolerated by premature infants, contain only 3·25-2·7 g. of protein (assuming that the protein content of human milk is 1·5 g. %).

Relation between Diet and Weight Gain. Gordon and his co-workers have continued their studies of the nutrition of premature infants by comparing the weight gained by premature infants receiving diets which differed in composition but were of equal caloric value (Gordon, Levine, and McNamara 1947). Table 2 gives the composition of the three feeds which were used and the average weight gained by babies in two weight groups between the seventh and the twenty-eighth day of life. The difference in the amount of weight which was gained on the three feeds is significant for the smaller but not for the larger infants. Thus the 31 smaller babies receiving a high protein, low fat intake (half-skimmed milk mixture) gained an average of 17·3 g./kg./day and this gain is of similar magnitude to that achieved by the foetus *in utero* during the eighth lunar month. The 14 infants in the same weight group receiving a moderately high intake of fat and protein (evaporated cow's milk mixture), gained an average of 14·9 g./kg./day, while the four receiving human milk (low protein and high fat) gained an average of 11·7 g./kg./day. In contrast the average rate of gain by the larger infants was similar for the three series receiving the different diets, and was approximately the same as that of the foetus during the ninth lunar month (Table 1). The rate at which weight was gained by both the smaller and the larger infants on all three diets, however, was high as judged by some textbook standards. This was probably due to the maintenance of a uniform caloric intake (120 cals./kg./day) which was achieved by giving feeds by gavage to infants who could not suck. The good progress of the smaller infants who were given the half-skimmed milk mixture led Gordon and his colleague to give it to a group of 11 very small infants, whose birthweights lay below 1,000 g. Their average gain between the seventh and twenty-eighth day of life was 17·6 g./kg./day and it is probable from the data in the report that they reached an average of 2,350 g. (a gain of 1,400 g.) by the end of nine weeks.

TABLE 2

RESPONSE TO DIFFERENT DIETS IN STUDY OF NUTRITION OF PREMATURE INFANTS (GORDON *et al.*, 1947)

Type of Food	Intake/Kg./Day					Average Weight Gain (G./Kg./Day)	
	Fluid (ml.)	Cals.	Protein (g.)	Fat (g.)	Carbo-hydrate (g.)	Birth weight (1,022 g.-1,621 g.)	Birth weight (1,622 g.-1,996 g.)
Half-skimmed milk with added carbohydrate	150	120	6·0	2·2	19·4	17·3 (31 infants)	14·2 (36 infants)
Evaporated cows' milk ..	150	120	4·8	5·5	12·9	14·9 (14 infants)	13·7 (25 infants)
Human milk	180	120	2·2	6·7	12·9	11·7 (4 infants)	12·7 (12 infants)

The rate of gain was therefore equal to that of the foetus during the later weeks of gestation.

Few paediatricians expect progress of the order which has just been described from very small premature infants during the early weeks of life. Hess and Lundeen (1941), for instance, consider that a daily weight gain of 5 to 10 g. is adequate for infants weighing less than 1,500 g. and believe that 'minimal feedings' are rewarded by good ultimate results. The premature infants under their care usually receive only 80 and never more than 100 calories/kg./day until they are one month old. The food is a mixture of three parts human milk and one part buttermilk in amounts which supply only 2-3 g. protein-kg./day, but water is given to raise the fluid intake to 160 ml./kg./day. Jorpes, Magnusson, and Wretlind (1946), using human milk alone in amounts to supply 100 cals./kg./day for feeding premature infants, also found that their patients gained weight slowly. Recently, these authors have supplemented human milk with a preparation of hydrolysed casein ('aminosol'), and infants receiving this diet have gained weight much more rapidly. Hydrolysed casein was found to be more effective than raw casein when the supplement given was 2·5 g./kg./day. Jorpes *et al.* (1946) now use human milk supplemented with 'aminosol' and glucose (2·5 g./kg./day of each) and have recorded that when this diet, in amounts to provide 120 cals./kg./day, was given to seven infants whose average birth weight was 1,354 g., an average gain of 654 g. was achieved during the first month of life. This compares well with the 510 and 690 g. gained by the foetus *in utero* during the eighth and ninth lunar months. A group of nine infants with an average birthweight of 1,962 g. gained 561 g., which does not compare so well with the 840 g. laid down by the foetus *in utero* during the later part of the ninth and early part of the tenth lunar months. Nevertheless, the weight gained by both groups of infants was nearly twice as great as that gained by the babies of similar birth weights who were given human milk alone in quantities to supply 100 cals./kg./day. Since it has been shown that premature infants receiving adequate diets will gain weight at a similar rate to the foetus *in utero* at corresponding weeks of gestation, it seems evident that this rate should be used as the standard in assessing the progress of these babies.

Our investigation was part of a trial which was planned by a committee appointed by the Medical Research Council. At the time when Magnusson (1944 and 1945) and Jorpes *et al.* (1946) reported the value of 'aminosol' for feeding premature infants were published, British preparations of hydrolysed casein had recently become available. It seemed rational to use predigested protein to supplement the protein intake of premature babies since, first, they have low gastric acidity (Miller, 1941) and the enzymic activity in the stomach, pancreas, and possibly the bowel is underdeveloped (Werner, 1948), and secondly they tend to vomit and to aspirate after feeding. Protein digests are composed of a mixture of polypeptides and amino acids which is freely soluble and can be absorbed by the alimentary tract without much digestive activity, and no curd is formed in the stomach. The present trial of hydrolysed casein was begun before the paper by Gordon *et al.* (1947) showing the value of half-skimmed milk mixtures for feeding young premature babies had been published, although Levine and Gordon (1942) had presented a preliminary report. The relative merits of predigested and whole milk protein have yet to be fully investigated.

Present Investigation

Grouping. All infants admitted to hospital were examined on the third day of life in order to assess their general condition, and any infant whose

condition was very poor or who had a congenital malformation was omitted from the investigation. The remainder were grouped according to their birth weight into the half-pound weight groups which are shown in Table 3.

TABLE 3

GROUPING OF PREMATURE INFANTS ACCORDING TO BIRTH WEIGHT

Group	Birth Weight (lb. oz. and g.)			
				G.
1		Under 3	0	Under 1,361
2	From 3	0	to 3	7¾ 1,361 – 1,580
3	„ 3	8	„ 3	15¾ 1,587 – 1,807
4	„ 4	0	„ 4	7¾ 1,814 – 2,034
5	„ 4	8	„ 4	15¾ 2,041 – 2,261

Feeds. In planning the investigation it was arranged that the diets which were already being used should be continued as a basis for the feeds to be given. An amount of casein hydrolysate to raise the protein concentration by about 2 g./100 ml. was to be added to the milk feeds of alternate infants, while control cases were to be given similar milk feeds which contained a 2% sugar supplement instead of the hydrolysate. Thus both groups were to receive diets of equal caloric value.

The composition of the milk feeds which were used at the beginning (Period I) of our investigation is shown in Tables 4 and 5. After the investigation had been in progress for nine months (January to October, 1946), it became apparent that the infants were not gaining as much weight during the first month of life as had been gained by infants who had been given the optimum diet used by Jorpes *et al.* (1946). The caloric intake of the babies in our series was lower during the first weeks of life, and this was thought to explain their lower weight gains. It was therefore decided to use feeds of higher caloric value by giving both the casein hydrolysate and the sugar supplement together in the milk mixtures which were being used. The composition of these feeds, which were used in the later part of our investigation (Period II), is shown in Tables 4 and 5 (see over). Evaporated and dried milk of known percentage composition was used, the same brands* being given to the infants throughout the investigation. Human milk was obtained locally and was not analysed. Two preparations of casein hydrolysate were supplied for the investigation, one by Ashe Laboratories Ltd. and the other by Genatosan Ltd. They contained similar amounts of protein but there were differences in the mineral composition (see Table 6), the most important being the lower

* 'Regal brand (Wilts United Dairies) full cream and half cream (Special), Cow and Gate.'

TABLE 6

COMPARISON OF MINERAL CONTENT OF 'ASHE' AND 'GENATOSAN' CASEIN HYDROLYSATE

	Casein Hydrolysate	
	'Ashe' (mg./10 g. hydrolysate)	'Genatosan' (mg./10 g. hydrolysate)
Total calcium (Ca.)	17–34	134
„ sodium (Na.)	12–23	15
„ potassium (K.)	Trace	40
„ chlorine (Cl.)	11–40	24
„ phosphorus (P.)	1–34	72

calcium content of the Ashe product. Fortunately, the change from 'Ashe' to 'Genatosan' hydrolysate was made at a time when the plan of the Birmingham investigation was being altered, and therefore the results could easily be separated. The 'Ashe' hydrolysate was used throughout the first period except for a week or two at the end when the supplies were exhausted, while 'Genatosan' was used throughout the second period.

PERIOD I. The plan was to give alternate infants in each weight group the protein supplemented feeds and the control feeds (Tables 4 and 5). A 5% glucose solution was to be given during the first 48 to 72 hours of life until milk feeds were begun. The infants were then to be given the control feeds until their daily fluid intake had reached 120 ml./kg. (2 oz./lb.), aiming to give this volume by the end of the first week. After this, the protein-supplemented feed was to be introduced for those infants who had been scheduled to receive it. The feeds were to be graded through the Stages 1 and 2 shown in Table 5, and the stronger Stage 3 feeds (Table 4) were usually to be given between the second and third week of life, depending upon the size and condition of the infant. Most of the smaller infants received the milk mixtures during the early weeks of life according to the plan. A few of the bigger (over 4 lb.) infants were fed from the breast, and many of them were given the full-cream dried milk mixture (1 in 16) from the start so that as soon as they were considered fit they could be sent home on an easily prepared diet. The percentage composition of this dried milk mixture is similar to that of the evaporated milk control feed. All the babies were given the dried milk mixture before their discharge from hospital, and the strength was subsequently increased from 1 in 16 to 1 in 12.

PERIOD II. The plan was to give all the infants the high protein and high calorie diets as soon as milk feeds were introduced on the second or third day of life and to grade the feeds through Stages 1 and 2 (Table 5) to full-strength (Table 4). It was decided to omit many of the infants who weighed over 4 lb. at birth from this part of the investigation so that a more detailed study of the smaller

TABLE 4

THE COMPOSITION OF THE FEEDS (STAGE 3)

		Diet	Milk Formulae		Cals./Oz.	Percentage Composition of Feeds			Calories and Protein (G.) supplied by 180 ml./Kg. (3 oz./lb.) per Day.		Percentage Distribution of Calories		
						P.	F.	C.	Cals./kg./Day	P./kg./Day	P.	F.	C.
FIRST PERIOD	Evaporated and human milk mixtures	HIGH PROTEIN containing 'Ashe' casein hydrolysate — Evaporated milk mixtures	Evaporated milk	2 oz.	17·5	4·0 (1·8 milk; 2·2 cas. hyd.)	2·0	7·1 (2·5 milk; 4·6 sugar)	112	7·2	26	29	45
			Water	8 oz.									
			Sugar	3½ dr.									
			Casein hydrolysate	7·75 g.									
		HIGH PROTEIN containing 'Ashe' casein hydrolysate — Human milk mixtures	Human milk	8¾ oz.	20	3·5 (1·3 milk; 2·2 cas. hyd.)	3·5	6·6	128	6·3	19	44	37
			Water	1¼ oz.									
			Casein hydrolysate	7·75 g.									
		LOW PROTEIN CONTROL — Evaporated milk mixtures	Evaporated milk	2 oz.	17·5	1·8	2·0	9·4 (2·5 milk; 6·9 sugar)	112	3·2	11	29	60
			Water	8 oz.									
			Sugar	5 dr.									
		LOW PROTEIN CONTROL — Human milk mixture	Human milk		20	1·5	4·0	7·5	128	2·7	8	50	42
	Dried milk mixtures for bigger babies	LOW PROTEIN CONTROL — 1-16 Full-cream dried milk mixtures	Full-cream dried milk	5 dr.	17	1·7	1·7	9·3 (2·4 milk; 6·9 sugar)	109	2·1	12	26	62
			Water	10 oz.									
			Sugar	5 dr.									
		1-12 Follow-up feed	Full-cream dried milk	6⅔ dr.	17·5	2·2	2·2	7·9 (3·1 milk; 4·8 sugar)	112	3·7	15	33	52
			Water	10 oz.									
			Sugar	3½ dr.									
SECOND PERIOD	Evaporated and human milk mixtures	HIGHER CALORIES AND HIGH PROTEIN Containing 'Genatosan' casein hydrolysate — Evaporated milk mixtures	Evaporated milk	2 oz.	20	4·2 (1·8 milk; 2·4 cas. hyd.)	2·0	9·4 (2·5 milk; 6·9 sugar)	128	7·6	23	25	52
			Water	8 oz.									
			Sugar	5 dr.									
			Casein hydrolysate	7·75 g.									
		HIGHER CALORIES AND HIGH PROTEIN Containing 'Genatosan' casein hydrolysate — Human milk mixtures	Human milk	10 oz.	24	3·9 (1·5 milk; 2·4 cas. hyd.)	4·0	8·9 (7·5 milk; 1·4 sugar)	154	7·0	18	41	41
			Sugar	1 dr.									
			Casein hydrolysate	7·75 g.									
	Dried milk mixture for bigger babies	HIGHER CALORIES AND HIGH PROTEIN Containing 'Genatosan' casein hydrolysate — Half-cream dried milk mixture	Half-skimmed dried milk	10 dr.	20	3·8	2·1	8·9 (5·5 milk; 3·4 sugar)	128	6·8	22	27	51
			Water	10 oz.									
			Sugar	2½ d.									

TABLE 5

THE COMPOSITION OF THE EVAPORATED AND HUMAN MILK MIXTURES (STAGES 1 AND 2)

		Diets	Cals./Oz.		Percentage Composition of Feeds : Stages 1 and 2						Calories and Protein (g.) supplied by 120–180 ml./kg. (2-3 oz./lb.) per day	
					P.		F.		C.		Stage 2 Feeds	
			Stage 1	2	Stage 1	2	Stage 1	2	Stage 1	2	Calories	Protein
FIRST PERIOD	HIGH PROTEIN containing 'Ashe' casein hydrolysate	Evaporated milk mixtures	8	14·5	1·9	3·4	0·8	1·3	3·4	6·7	62–93	4·1–6·1
		Human milk mixtures	12	17	1·7	3·2	1·3	2·8	5·5	6·7	73–100	3·8–5·7
	LOW PROTEIN control	Evaporated milk mixtures	9	14·5	0·8	1·2	0·8	1·3	5·7	9·0	62–93	1·4–2·2
		Human milk mixtures	10	15	0·8	1·1	2·0	3·0	3·8	6·6	64–96	1·3–2·0
SECOND PERIOD	HIGHER CALORIES AND HIGH PROTEIN containing 'Genatosan' casein hydrolysate	Evaporated milk mixtures	10·5	17	2·0	3·6	0·8	1·3	5·7	9·0	73–109	4·3–6·5
		Human milk mixtures	17	21	1·9	3·6	1·6	2·5	6·9	9·1	90–135	4·3–6·5

premature babies could be made. With the exception of three who were breastfed, the infants all received the higher calorie and high protein diets. Some of those weighing over 4 lb. at birth were given the half-skimmed milk mixture from the start, but its percentage composition was similar to that of the evaporated milk mixture containing casein hydrolysate. All the babies were given the dried milk mixture before their discharge from hospital. They were usually changed on to a full-cream dried milk mixture as soon as they weighed 8 lb.

Vitamin and Iron Supplements. The infants in hospital were given vitamin and iron supplements as follows:

Vitamins

Ascorbic acid 50-100 mg. daily from three days of age.

'Tab. benerva co.' { Aneurin 1 mg. / Riboflavine 1 mg. / Nicotinic acid amide 15 mg.

½-1 tab. daily from three days of age.

A and D concentrates, 'adexolin' or 'radiostoleum'

12,000 I.U. vit. A, 3,000 I.U. vit. D } daily from two weeks of age.

Iron

Mist. ferrous sulph. containing ferrous sulph. (crystalline) 5 gr. to 1 dr., small doses daily from six weeks of age, increasing to 1 dr. (Period I).

Mist. ferri et ammon. cit. containing ferri et ammon. cit. 5 gr. to 1 dr., small doses daily from two weeks of age increasing to 1 dr. (Period II).

After discharge from hospital, orange juice was gradually substituted for the ascorbic acid, and codliver oil for the fat-soluble vitamin concentrate.

Records and Follow-up Care. Full clinical records were kept of the progress of the infants throughout their stay in hospital, and these were continued at special follow-up clinics. Return visits at two-weekly intervals until three months, monthly until six months, and then at nine months and one year of age, were requested. Unfortunately attendances were often irregular. The patients were weighed twice weekly while in hospital and subsequently at the follow-up clinics. Advice about diet and about vitamin and iron supplements was given at the return visits, and the infants were usually allowed to start on a mixed diet at four to six months of age.

Samples of blood for serum protein and haemoglobin estimations were usually taken from the

infants in the ward at two-weekly intervals during the first part, and at weekly intervals during the second part of the investigation. Further samples were obtained at the follow-up clinic. Satisfactory samples were not always secured and therefore the number of results from individual infants has varied.

Methods of Analysis. Haemoglobin was estimated in the Evelyn photoelectric colorimeter against a standard curve based on Van Slyke's oxygen capacity determination using the commonly accepted value of 1·34 ml. of oxygen/g. Hb. (100%=13·8 g. haemoglobin/100 ml.). The serum protein and non-protein nitrogen levels were estimated by micro-Kjeldahl digestion followed by direct nesslerization as described by Hickmans (1948). Broadbent and Finch (data to be published) have compared the average results for serum protein concentrations obtained by this method with those obtained by a titration method and have found that they are lower by about 0·25 g. protein/100 ml. serum.

Subjects for the Investigation. During the period September, 1945, to October, 1947, 203 premature infants admitted to the City of Birmingham Premature Infant Unit (the Sorrento) or to the Birmingham Children's Hospital were included in the investigation. Fifty-five were omitted from the final analysis of the results for the following reasons:

General condition had deteriorated between the third and seventh day	16
Infections contracted during the investigation	27
Not been kept on the diet (usually to hasten discharge from hospital)	12

The remaining 148 infants received the following diets:

PERIOD I	
HIGH PROTEIN (H.P.) DIETS	
Evaporated milk mixtures containing 'Ashe' casein hydrolysate	28
Human milk mixtures containing 'Ashe' casein hydrolysate	1
LOW PROTEIN (L.P.) DIETS	
Evaporated milk mixture control feed	32
Full-cream dried milk (1 in 16) mixture	17
PERIODS I AND II	
Human milk (alone or complemented with control feed)	17
PERIOD II	
HIGHER CALORIE AND HIGH PROTEIN (H.C.P.) DIETS	
Evaporated milk mixture containing 'Genatosan' casein hydrolysate	39
Human milk mixture containing 'Genatosan' casein hydrolysate	11
Half-cream dried milk (1 in 8) mixture	3

Fourteen of the infants who received the high protein and low protein diets at the beginning of the first period were given considerably lower intakes of calories than the others, because the more dilute evaporated milk mixtures (Stages 1 and 2) were continued for a longer time. The results from this small series of infants receiving lower calorie diets have therefore been assessed separately. They will be referred to as the preliminary series observed during the first period.

Results

The effect of the diets shown in Tables 4 and 5 has been assessed by comparing the average weekly gain in weight and the serum protein and haemoglobin levels of the infants receiving them. The progress of the infants in each of the five weight groups has been considered separately. Twenty-six of the 148 infants have been excluded from this analysis because in some groups the number of infants receiving the same diets was too small to average. For instance, Group I included only ten babies, and therefore each of the diets was given to a few infants only. The average weight curves and the serum protein levels of the infants in Groups 2-5 seemed to show that the progress and nutrition of the smaller babies was more affected by diet than was that of the bigger infants. The individual weight curves of all the babies in Groups 1 and 2 have therefore been studied in detail.

Average Intake of Food. Table 7 shows the average amounts of food ingested by the infants in Groups 2-5 whose weekly weight gains have been included in the construction of the average weight curves. In estimating the intake of food by each infant allowances have not been made for the slight inevitable losses due to small amounts clinging to the bottles and teats or spilt on the bed linen. These have been estimated to be of the order of 5% (Gordon *et al.*, 1940). If an infant vomited, however, an estimate of the amount was made and deducted from the intake for the day. It can be seen that an intake of 120 calories/kg./day was usually reached by the third week of life for the infants observed in the second part of the investigation, but not until the fourth week for those in the first part. The intake of calories was also higher during the second week of life for those in the second period. It is apparent that the average intakes of the infants observed in both periods later reached a somewhat higher level than would have been expected from the feeding schedules shown in Table 4. This was chiefly due to the fact that larger volumes of food than 3 oz./lb./day was given to many of the infants because they seemed hungry and were able to tolerate more food.

Gain in Weight. A curve representing the gain in weight of the foetus during the last three months of gestation has been drawn using the figures for the weight of the foetus at different ages given by Huggett (1946). This curve has been made the basis of comparison for the weight curves of premature infants at corresponding weeks of gestation. Other authors (Streeter, 1920; Crosse, 1945; Anderson, 1946) have presented different figures for the weight of the foetus and if the average of the available data had been used, the curve would have been slightly higher but of similar shape to the one which is shown in the diagrams.

TABLE 7

AVERAGE INTAKES OF INFANTS IN GROUPS 2, 3, 4, and 5 FED ON DIETS USED IN THE FIRST AND SECOND PERIODS OF THE INVESTIGATION

Weeks			1 (5 days)			2			3			4			5			6			7			8			9		
	Diet	No. of Infants	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg.Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day	Cals./Kg./Day	G. of P./Kg./Day	Total G. of P./Day
Group 2	Period I. H.P.E.	5	36	1·0	1·5	85	5·1	7·7	104	7·1	11·3	122	8·0	13·8	126	8·1	15·1	123	7·7	15·4	123	6·6	14·1	124	5·0	13·1	142	5·3	13·2
Birth weight 3·0–3·7¾ lb.	Period I. L.P.E.	6	27	0·5	0·8	88	2·1	3·0	117	3·1	4·7	123	3·5	5·8	121	3·5	6·4	114	3·0	6·5	122	3·5	7·5	117	3·5	8·0	115	3·9	9·7
(1361–1580 G.)	Period II. H.C.P. (E. and H.)	10	45	1·9	2·7	101	4·8	7·0	136	6·2	8·8	144	7·1	12·2	141	7·2	13·6	143	7·1	15·2	135	7·2	17·0	135	7·3	19·4	146	7·9	22·7
Group 3.	Period I. H.P.E.	8	31	0·7	1·2	91	4·1	6·6	115	6·5	11·4	121	7·1	14·7	125	6·8	14·0	122	5·9	13·2	125	5·8	14·7						
Birth weight 3·8–3·15¾lb.	Period I. L.P.E.	10	32	0·7	1·1	93	2·2	3·6	121	3·2	5·7	123	3·4	5·6	118	3·2	6·8	122	4·0	9·2	121	4·6	10·6						
	Periods I and II. L.P.H.	6	43	1·1	1·5	100	2·0	3·3	133	3·0	5·4	130	2·8	5·4	122	2·7	5·5												
(1587–1807 G.)	Period II. H.C.P. (E. and H.)	18	41	1·8	2·8	104	4·5	7·0	128	6·4	10·9	143	7·0	13·4	139	7·3	15·0	139	7·6	17·2	140	7·3	19·0						
Group 4.	Period I. H.P.E.	9	38	1·0	1·9	86	4·3	7·9	112	5·9	11·4	127	6·9	13·9	126	6·3	14·6												
Birth weight 4·0–4·7¾ lb.	Period I. L.P.E.	7	40	0·8	1·5	95	2·1	4·0	118	3·0	6·1	118	3·1	6·7	140	3·1	7·2												
(1814–2034 G.)	Period I. L.P.D.	7	45	1·2	2·2	106	2·8	5·4	117	3·3	6·3	114	3·2	7·0	119	3·7	7·5												
	Period II. H.C.P. (E. and H.)	11	45	1·9	3·4	108	4·6	8·4	138	6·7	11·8	140	6·6	13·8	144	7·8	17·6												
Group 5.	Period I. L.P.D.	10	36	1·0	1·9	101	2·6	5·2	115	3·0	6·6	113	3·1	7·8	117	4·1	10·1												
Birth weight 4·8–4·15¾ lb.	Periods I and II. L.P.H.	6	BREAST FED						–			–			–														
(1041–2261 G.)	Period II. H.C.P. (E. and D.)	9	39	1·6	3·4	100	4·5	9·2	132	6·5	14·3	138	7·1	16·8	142	7·5	19·9												

H.P.E.=High protein evaporated milk mixtures containing ' Ashe ' casein hydrolysate.
L.P.E.=Low protein evaporated milk mixtures control feed.
H.C.P. (E. and H.)=Higher calorie and high protein (evaporated milk mixture or human milk mixture containing ' Genatosan ' casein hydrolysate).
L.P.H.=Low protein human milk (alone or complemented with control feed).
L.P.D.=Low protein full-cream dried milk (1 in 16) mixture.
H.C.P. (E. and D.)=Higher calorie and high protein (evaporated milk mixture containing ' Genatosan ' casein hydrolysate or half-cream dried milk (1 in 8) mixture).

Average Weight Curves. The average weight curves of the infants in Groups 2-5, who received the diets in the amounts recorded in Table 7, are shown in Fig. 1.

GROUPS 3-5 (BIRTH WEIGHT 3½-5 lb.). The average curves for the larger infants will be described first, since they appear to be similar to each other for all the diets which were used (Fig. 1*b*, 1*c*, 1*d*). After an initial loss of weight during the first week and slow gains during the second and third weeks, the weekly rate increased, becoming equal to the amount which is gained by the foetus *in utero*. This is well shown by the slope of the weight curves which is parallel to that of the 'standard' growth curve. It may be concluded therefore that the diets used in both parts of this investigation provided sufficient food to enable the bigger infants to grow at the 'normal' rate for their age of gestation.

GROUP 2 (BIRTH WEIGHT 3-3½ lb.). In contrast, the average weight curves of the smaller infants (Fig. 1*a*) appear to have varied according to the diets which they were receiving. Thus the infants who were receiving higher intakes of calories in diets containing 'Genatosan' casein hydrolysate (H.C.P.) during the second part of the investigation, gained more weight between the ages of four and eight weeks than did those receiving either the high protein diet containing 'Ashe' casein hydrolysate (H.P.) or the low protein control diets (L.P.) during the first part of the investigation. Since their weight curve is parallel to the standard, it is evident that the faster rate of gain achieved by the infants in the second period of the investigation resembles that of the foetus *in utero* and that of all the bigger infants (Figs. 1*b*, 1*c*, and 1*d*). The slower rate of gain by the infants in the first period may therefore be regarded as unsatisfactory and probably due to insufficient food.

Individual Weight Curves. Since the smaller (Group 2) infants showed differences in weight gain which might be attributed to the diets which they were receiving (a finding which is in keeping with the observations made by Jorpes *et al.* (1946) and by Gordon *et al.* (1947)), the gain in weight of the individual babies in this weight group and in Group 1 have been studied and their weight curves are shown in Figs. 2 and 3. Figs. 2*a*, 2*b*, 2*c* show the individual, and Fig. 2*d* the average (repeated from Fig. 1*a*) weight curves of the infants in Group 2. Again, it can be seen that weight was gained more uniformly and often at a higher rate by the infants who were receiving the higher calorie and high protein (H.C.P.) diet of the second period (Fig. 2*c*) than by those who were receiving either of the diets (high protein or low protein control) of the first period (Figs. 2*a* and 2*b* respectively). Thus the average weight curves (Fig. 2*d*) are representative of the progress of most of the individuals.

For comparison, the curves of the six infants in this weight group who received the lower calorie intakes (three high and three low protein control diets) of the preliminary series have been graphed and they are shown as dotted lines in Figs. 2*a* and 2*b*. Table 8 shows the average daily intakes of these six babies during the early weeks of life, and they are seen to be much lower than the intakes (Table 7)

TABLE 8

AVERAGE INTAKES OF SIX INFANTS IN GROUP 2 ON LOW CALORIE (STAGE 2) FEEDS

	High Protein Diet (3 Infants)			Low Protein Diet (3 Infants)		
Week	Cals./kg./Day	Protein g/kg./Day	Total Protein (g) Day	Cals./kg./Day	Protein g./kg./Day	Total Protein (g) Day
1	34	0·7	0·9	34	0·6	0·8
2	81	3·7	4·7	58	1·6	2·0
3	103	6·1	8·5	89	1·7	2·6
4	86	6·2	9·6	90	2·2	3·0
5	89	6·7	10·8	87	2·2	3·2
6	103	7·4	12·9	90	2·2	3·5
7	112	4·4	8·2	98	2·3	3·9

of the other infants in Group 2. The weight curves of the infants who were receiving the lower calorie and high protein intakes are seen to lie within the same range as those of the infants who received a higher intake of calories during the first period (Fig. 2*a*), but the infants who were receiving the lower calorie and low protein intakes are seen to have gained at a slower rate (Fig. 2*b*). The low protein control diet used for the preliminary series in the first period supplied an average of only 90 calories and 2·2 g. protein/kg./day by the sixth week (Table 8), so that the slow progress of the babies who were receiving it is easily explained. It is interesting to note that those on a low calorie but higher protein intake were able to gain more rapidly.

GROUP 1 (BIRTH WEIGHT LESS THAN 3·0 lb.). A relationship between diet and weight gain is also apparent from the progress of the ten smaller (Group 1) infants. The group consisted of four infants with birth weights between 2 and 2½ lb., all of whom were observed in the first period, and of six infants with birth weights between 2½ and 3 lb., one of whom was observed during the first, and five in the second period. The weight curves are shown in Figs. 3*a* and 3*b*. It can be seen at once from Fig. 3*a* that none of the infants under 2 lb. 8 oz. gained weight at the standard rate during the early weeks of life. Yet in the series of Gordon *et al.*

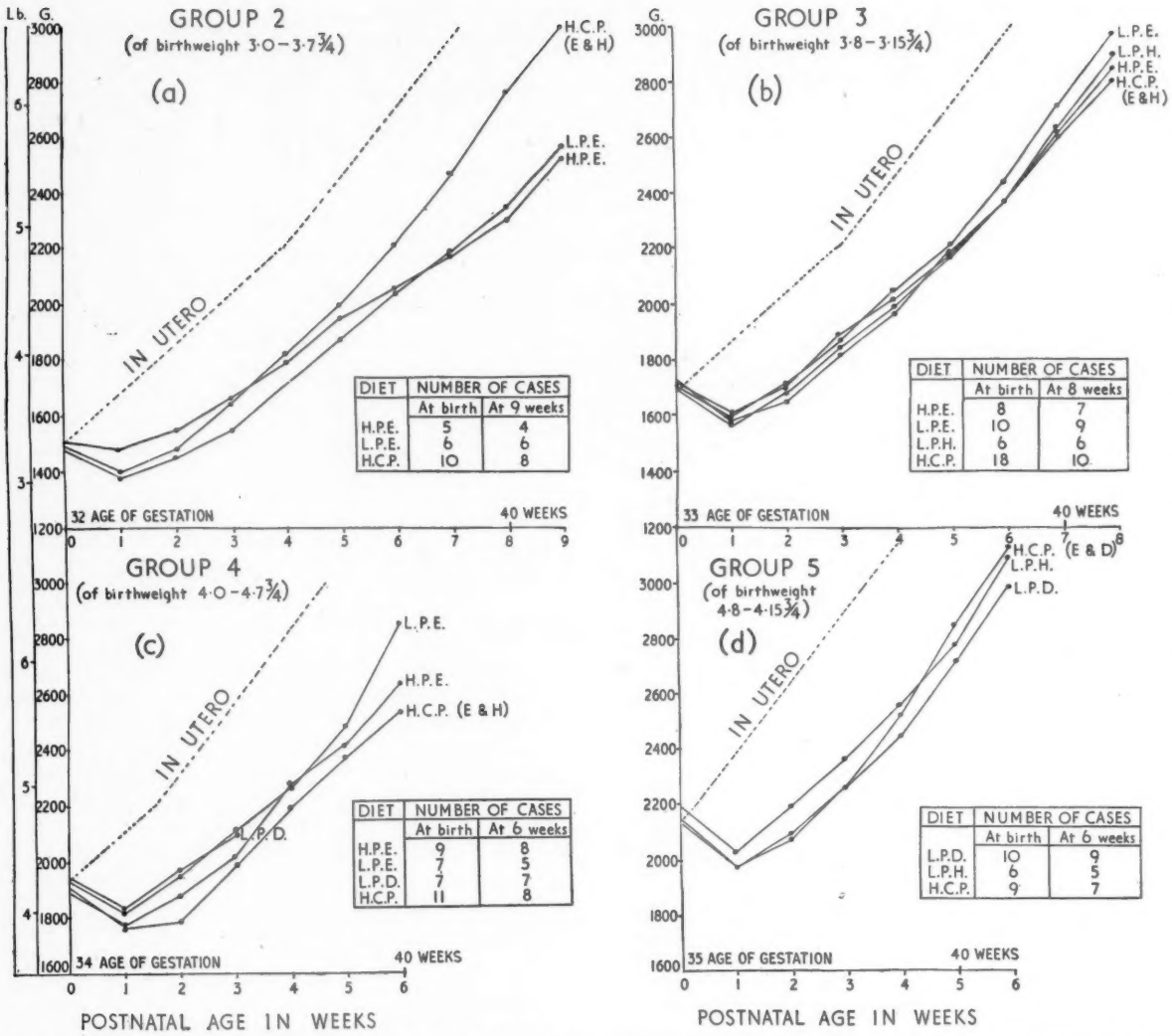

FIG. 1.—In each of the weight groups 2, 3, 4 and 5 (1*a*, 1*b*, 1*c* and 1*d* respectively), the average weight curves of series of infants who received the different diets are shown for comparison with each other and with the curve of the foetus at the same age of gestation.

H.P.E. = high protein
L.P.E. = low protein control } Period I.
L.P.D. = low protein control
L.P.H. = low protein. Periods I and II.
H.C.P. = higher calorie and high protein (Period II)

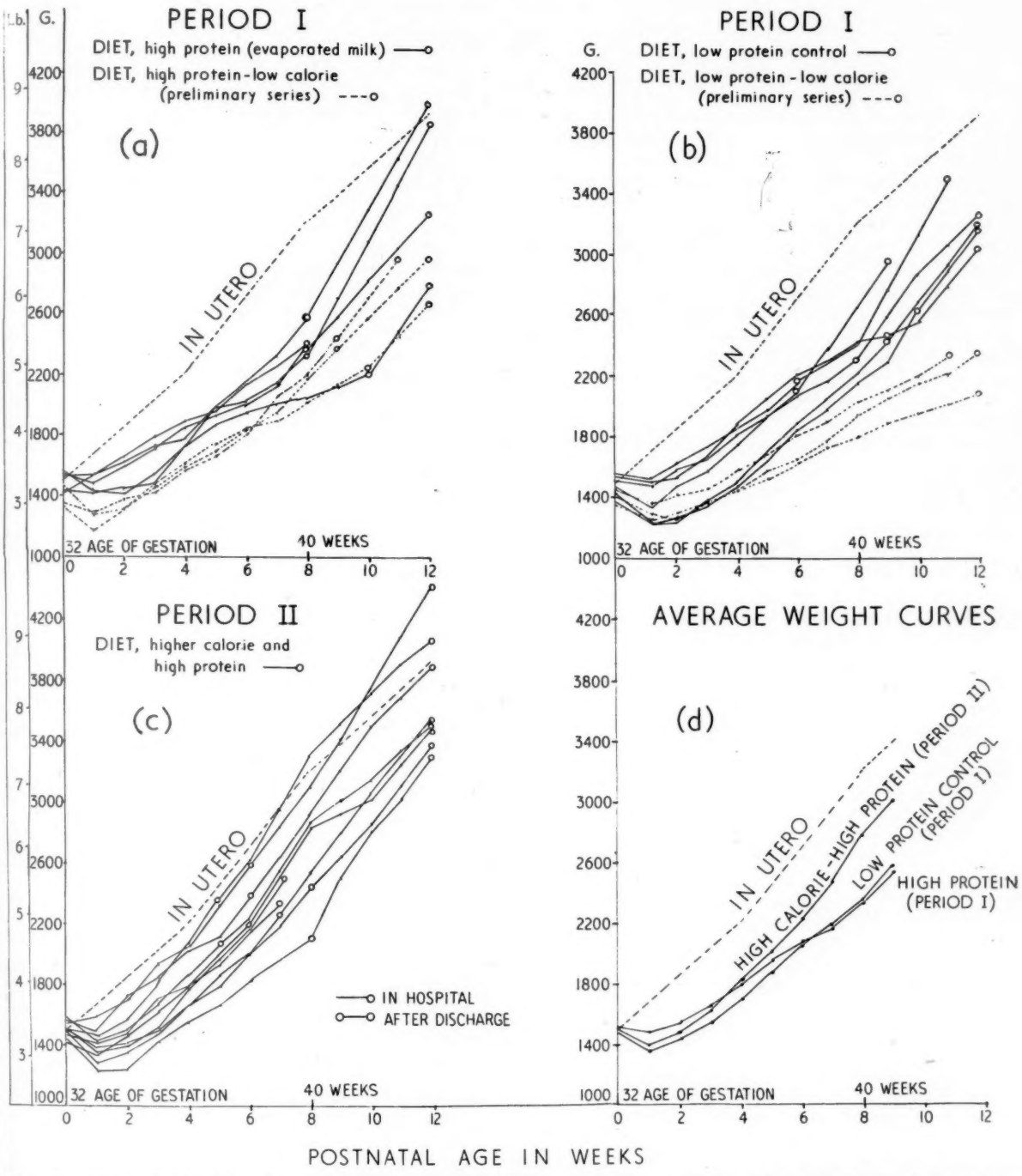

FIG. 2.—The individual (2*a*, 2*b*, 2*c*) and the average (2*d*) weight curves of the infants in Group 2 have been arranged according to the diets which they received. The individual curves of infants receiving the low calorie diets of the preliminary series have been graphed for comparison in 2*a* and 2*b*, but they have been omitted in computing the average curves (2*d*).

(1947) nine infants with similar birthweights who were fed on the half-skimmed milk mixture were able to do so, and their average weights at four and nine weeks of age have been graphed for comparison.

The diets given to the smaller infants in Group 1 (birth weight 2 lb. 0 oz. to 2 lb. 7¾ oz.) in our investigation were as follows: one baby received human milk, one baby received human milk with the addition of ' Ashe ' casein hydrolysate, and two were fed on the lower calorie, low protein control diets of the preliminary series in the first period. None of the infants received as high an intake of calories during the second week as the subjects investigated by Gordon *et al.*, and only A.H. had an intake which reached 120 cals./ kg./day at four weeks of age. This baby also had a higher protein intake than the others, a fact which will be referred to again when the serum protein levels are being discussed.

The bigger infants in Group I (birth weight 2 lb. 8 oz. to 2 lb. 15¾ oz.) all received the higher calorie and high protein of the second period, with the exception of Baby G. who was given the low protein control diet of the first period. The weight curves depicted in Fig. 3*b* show that this baby gained weight much more slowly than the rest, while the weight curves of the five infants who were observed in the second period are seen to be parallel with the standard curve from the second week of life onwards. It is of interest to note that two of these infants were receiving the evaporated milk, and three the human milk feeds (both of which contained ' Genatosan ' casein hydrolysate), and that the rate of gain was similar whichever feed was being used. The two diets appear therefore to have been of equal value in promoting gain in weight, but this should not be taken to imply that human milk is without advantages for premature infants.

It seems evident from the present study of the progress of premature infants that the growth of the smaller, but not that of the bigger infants, was affected by the diets which were given. The larger babies were probably able to obtain sufficient food by ' demand ' soon after birth and, because they were at a more advanced stage of development than the smaller ones, any minor deficiencies which may have been present in their diets did not cause retardation of their rate of growth. It is unfortunate that no babies weighing between 2 and 2½ lb. at birth were observed during the second period of the investigation and that therefore weight curves of very small infants receiving our 'optimum' higher

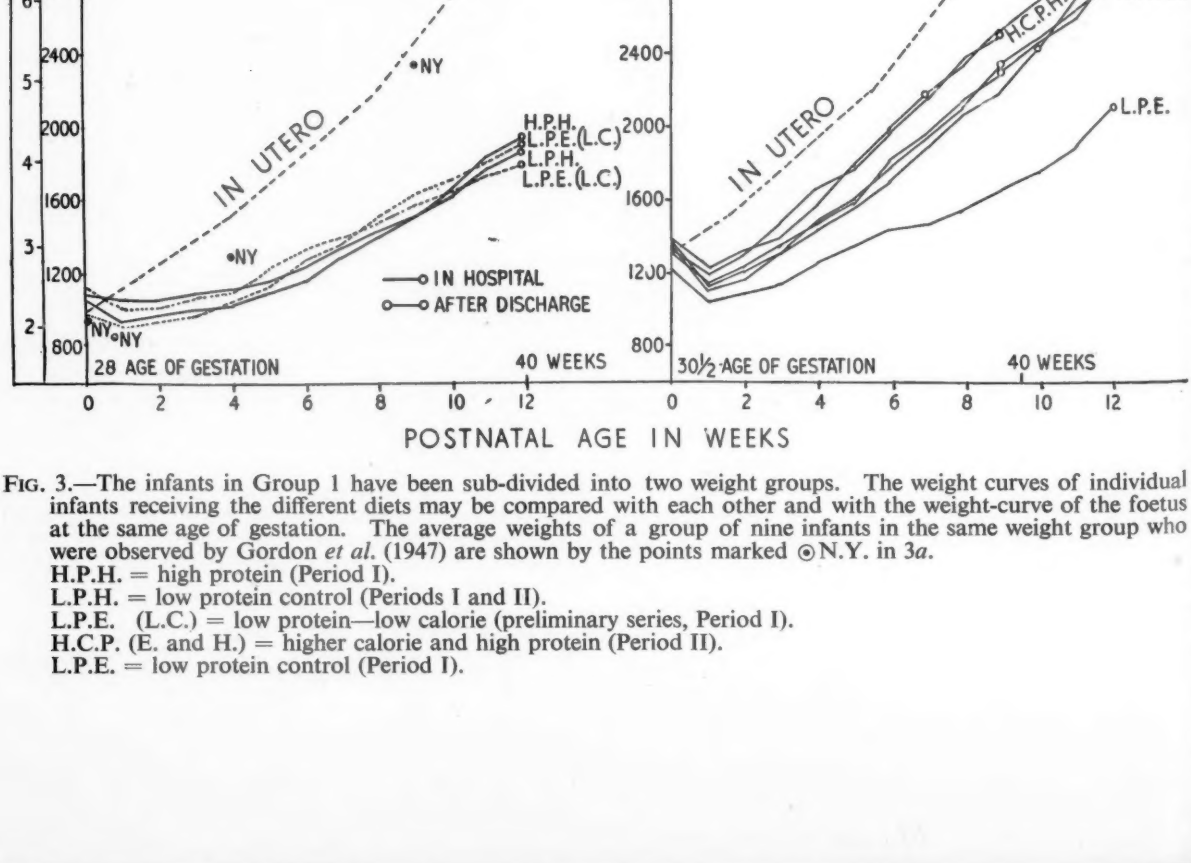

FIG. 3.—The infants in Group 1 have been sub-divided into two weight groups. The weight curves of individual infants receiving the different diets may be compared with each other and with the weight-curve of the foetus at the same age of gestation. The average weights of a group of nine infants in the same weight group who were observed by Gordon *et al.* (1947) are shown by the points marked ⊙N.Y. in 3*a*.
H.P.H. = high protein (Period I).
L.P.H. = low protein control (Periods I and II).
L.P.E. (L.C.) = low protein—low calorie (preliminary series, Period I).
H.C.P. (E. and H.) = higher calorie and high protein (Period II).
L.P.E. = low protein control (Period I).

calorie and high protein diet are not available for comparison with the progress made by the series of small premature infants (Gordon *et al.*, 1947).

Serum Protein Levels. The serum protein levels of the infants observed in the second period have been analysed first, since these infants all received the same diet and samples of blood were obtained from them at more frequent intervals than from those observed during the first period of the investigation. The average results of this later period have then been used as standards with which to compare the levels obtained in the earlier period. Figs. 4, 5, and 6 show the scatter and the averages for the total serum protein, albumin, and globulin levels respectively, of infants weighing between 3 and 5 lb. at birth who were observed during the second period. A comparison of the average levels of the infants in these three weight groups with those of full-term infants (Poyner-Wall and Finch, data to be published) at similar ages after birth is shown in Figs. 4*d*, 5*d*, and 6*d*. The scatter diagrams show that the range and distribution of the total serum protein levels are similar in all three weight groups of premature infants (Figs. 4*a*, 4*b*, 4*c*). The average levels are therefore approximately the same from week to week (Fig. 4*d*). Thus there is no apparent relationship between maturity (judged by birth weight) and the serum protein levels. Rimington and Bickford (1947) have shown that the serum protein levels in cord blood tend to increase with ' gestational ' age and it seemed probable that the levels of premature infants would also be found to vary with their maturity at birth. The range for the birth weights of the infants in the present investigation may not have been wide enough for this relationship to be shown. Differences in birth weight between 3 and 4½ lb. represent only four weeks of ' gestational ' age, and the estimation of age by birth weight can only be made approximately to within three weeks (Streeter, 1920). If results from a larger number of infants weighing less than 3 and more than 5 lb. at birth had been available for analysis a relationship between the serum protein levels and maturity at birth might have been apparent.

Fig. 4*d* shows that the average serum protein levels for all three groups of premature infants were significantly lower than those of full-term infants during the first ten weeks of life. This difference was due to both the albumin and globulin fractions being low. Thus it can be seen from Figs. 5 and 6 that the range and distribution (Figs. 5 and 6 *a*, *b*, *c*) and the average (Fig. 5 and 6*d*) for both the albumin and globulin levels of the premature infants in all three weight groups were similar to each other, but that they were all lower than those of the full-term infants in Poyner-Wall and Finch's series. The globulin levels were relatively lower as a percentage of the full-term infants' levels than the albumin levels. These low levels confirm the observations made by Darrow and Cary (1933) and by Rapoport, Rubin, and Chaffee (1943). Other previous observers (Utheim, 1920; Bridge, Cohen, and McNair Scott, 1941; Hickmans, Finch, and Tonks, 1943) have found that the serum protein levels of premature infants are lower than those of full-term infants in the early weeks of life, but few details regarding the weight at birth and none about the diet of the infants are given in their reports. The premature infants who were the subjects in this part of our investigation were all receiving the high protein and relatively high calorie diet of the second period and therefore their low serum protein levels (compared with those of full-term infants) are unlikely to have been due to malnutrition. It has been noted that any infant who had a low level at two weeks of age usually maintained a low level for several weeks. Low serum protein levels have been found also in a proportion of infants born at term (Trevorrow *et al.*, 1941; Poyner-Wall and Finch, data to be published) and it seems probable that they are due to a poor ability for generating plasma protein. Premature infants tend to have a poor response, but at three months of age their average serum protein levels are similar to those of full-term infants.

Fig. 7 shows the scatter of the total serum protein levels of the infants observed in the first period of this investigation compared with the average levels of those observed in the second period. The levels of the bigger infants (birth weight over 3½ lb.) shown in Figs. 7*c* and 7*d* will be described first (cf. weight curves in Fig. 1). The range and distribution of these serum protein levels is seen to be approximately the same for infants who were given the high protein and the low protein control diets, and the scatter lies equally above and below the average levels of the infants receiving the higher calorie and high protein diets of the second period. The levels of the infants who were breast-fed lay within the same range, but these have not been charted in order to simplify the diagrams. The albumin and globulin levels, estimated on the same samples as were used for total serum protein, were also found to be similar to those of the infants on the optimum diet. The findings show that the serum protein levels of the infants in these weight groups were unaffected by the differences in the diets used in the first and second periods of our investigation.

Figs. 7*a* and 7*b* show the levels of the infants in Group 2 (birth weight 3-3½ lb.), those recorded in Fig. 7*b* belonging to infants in the preliminary series who received lower calorie intakes (cf. weight curves in Fig. 2). Again a contrast with the findings from the bigger babies is shown, for the serum protein levels of the smaller (Group 2) babies appear to vary with the diets which were being given. Thus it can be seen in Fig. 7*a* that the levels of the infants receiving the high protein diet, tend to be higher than those of babies on the low protein control diets, and that many of the low levels are far below the average for the infants receiving the higher calorie and high protein diets of the second period. Fig. 7*b* shows that the serum protein levels of the infants who were receiving the lower calorie feeds

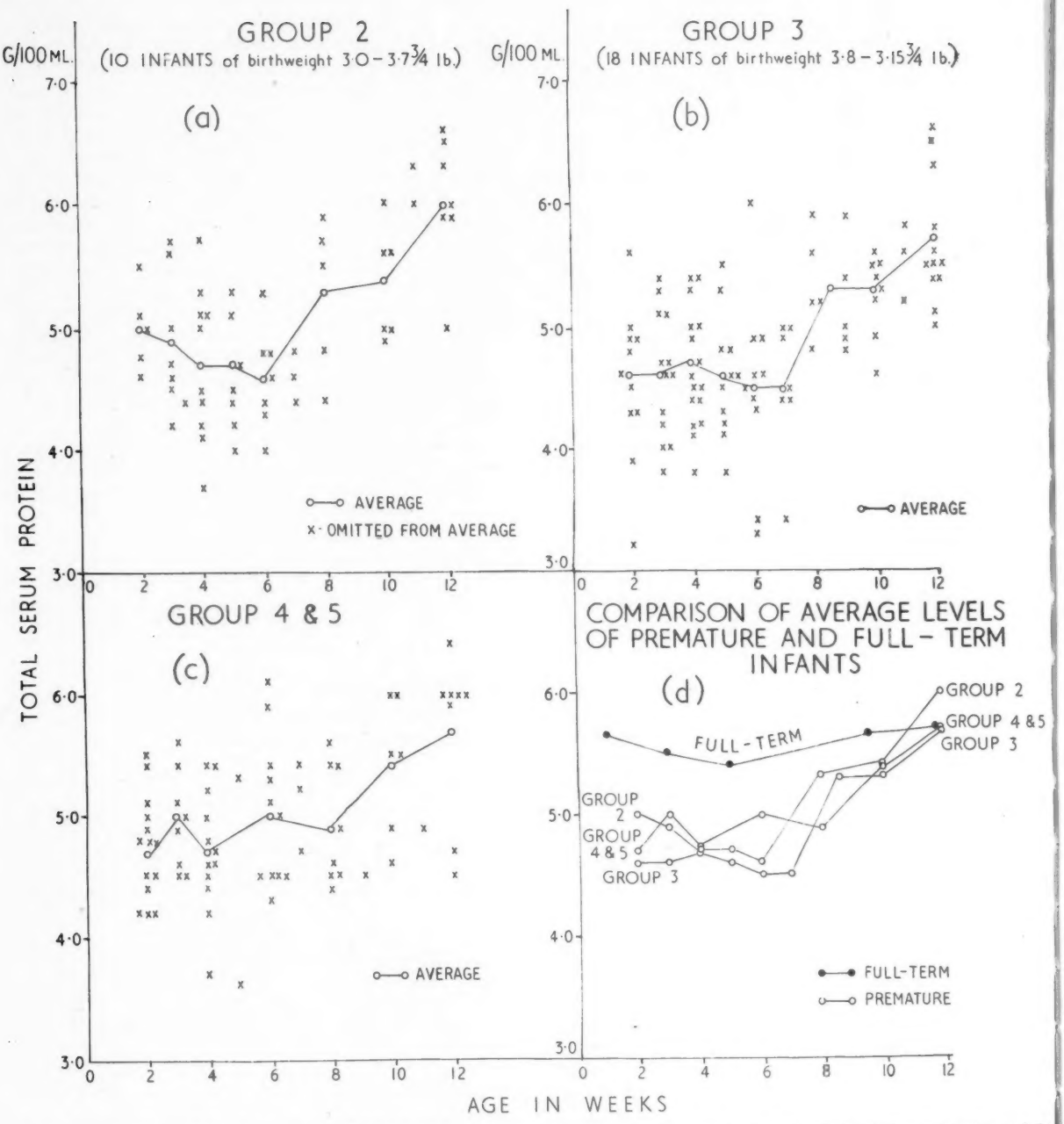

FIG. 4.—4*a*, 4*b*, and 4*c* show the individual and the average total serum protein levels of the infants in the weight groups 2, 3, and 4+5 respectively. The average levels for these groups are also shown in 4*d* for comparison with each other and with the average levels for full-term infants. The optimum diet was the higher calorie and high protein diet of Period II.

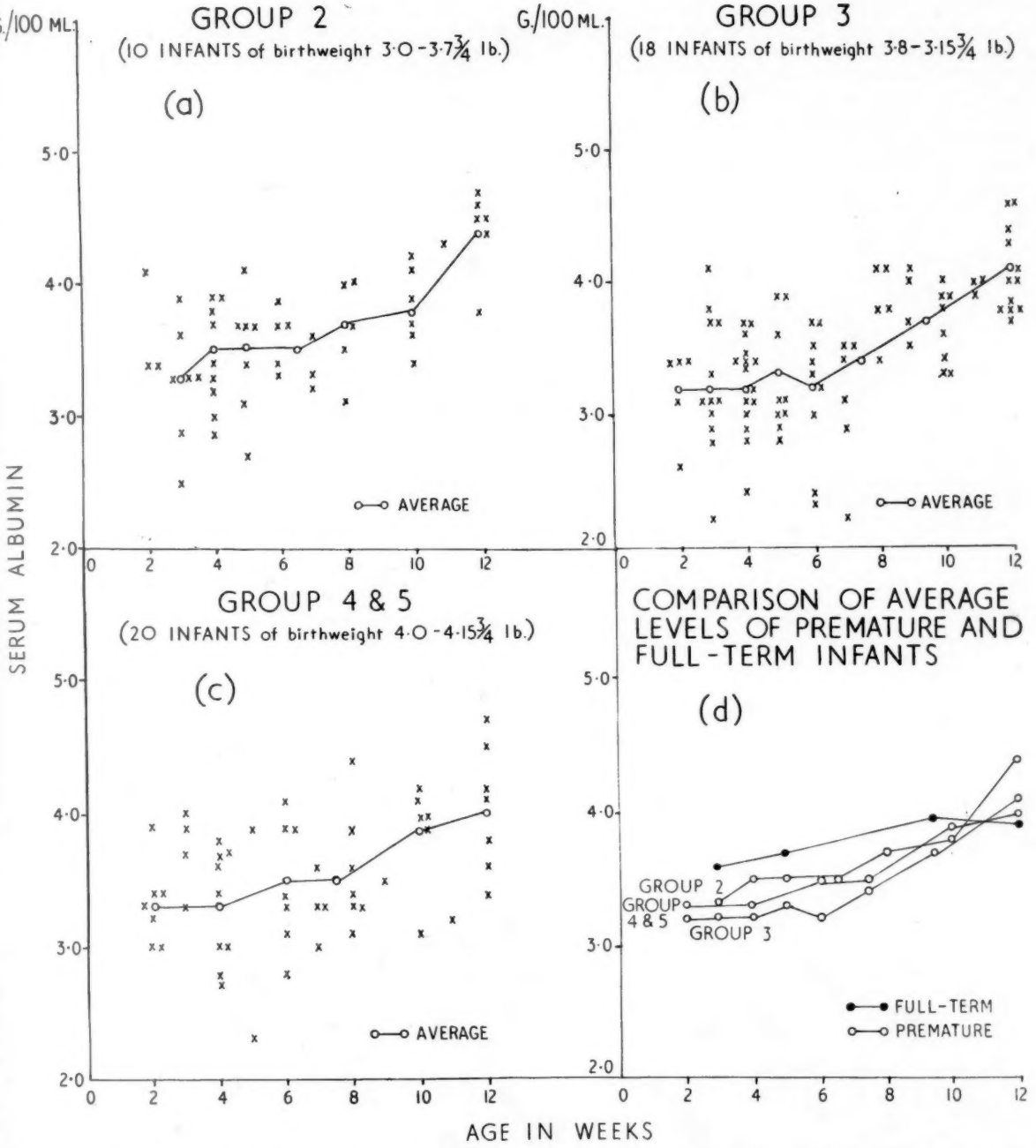

FIG. 5.—*5a*, *5b*, and *5c* show the individual and the average albumin levels of the infants in the weight groups 2, 3, and 4+5 respectively. The average levels for these groups are also shown in *5d* for comparison with each other and with the average levels for full-term infants. The optimum diet was the higher calorie and high protein diet of Period II.

of the preliminary period (whether high or low in protein) were nearly all below the average levels of the second period. This finding suggests that both the low calorie diets were deficient, and that hypoproteinaemia, probably due to undernutrition, had occurred despite the relatively high protein intake of the infants receiving the low calorie high protein diet. It is interesting to note, however, that the weight curves of these infants were higher than those of the infants receiving the low protein diet (see Figs. 2*a* and 2*b*). The albumin and globulin levels estimated on the same samples as were used for total serum protein show that the low total levels, which have just been described for some of the infants in Group 2 who were observed during the first period, were usually due to the albumin fractions being low. This finding lends support to the view that the hypoproteinaemia of these cases was due to nutritional deficiency. The results obtained from the few infants weighing less than 3 lb. at birth (Group 1) are in agreement. Thus all three infants in Group 1 (birth weight 3-3½ lb.) who received the low protein diets had much lower serum protein levels during the early weeks of life than A.H., who received human milk with added casein hydrolysate (Ashe), and the one infant in Group 1 (birth weight 2½-3 lb.) on the low protein control diet, had lower levels than the five on the higher calorie and high protein diet. Moreover, the average levels of these five infants, and A.H's levels, were as high as the average levels of the bigger babies and therefore may be regarded as indicating a good nutritional status.

Haemoglobin Levels. The haemoglobin levels of the premature infants observed in this investigation were analysed in the same way as their weight curves and serum protein levels, i.e. according to birth weight and to the diets which they received. The results show that the range and distribution of the haemoglobin levels of the infants in Groups 2-5 (excluding the infants in the preliminary series of the first period) were alike for the series of infants receiving each of the three diets shown in Table 7. Since the levels appear to have been unaffected by diet, they have all been averaged together in each weight group and the findings are shown in Table 9. It can be seen that the average levels of the infants were alike in the four groups of babies whose birth weights ranged between 3 and 5 lb. All the levels of the infants in these weight groups have therefore been averaged together and the results are also shown in Table 9. A previous study of the haemoglobin levels of premature infants according to weight at birth has been made by Mackay (1935) and she also obtained similar levels in each weight group. Furthermore the curve described by the average levels of all the infants in Groups 2-5, is like the one recorded by Mackay for the haemoglobin levels of premature infants whose birth weights lay between 3 and 5 lb. Mackay used the Haldane method for estimating haemoglobin, the levels being matched against a standard by direct vision. In discussing her results she notes that the levels of the infants in her series were higher than those recorded by other observers and suggests that the incidence of anaemia in premature babies may partly depend upon the diets which they receive.

Like the serum protein levels, the haemoglobin levels of the infants in Groups 1 and 2 who were given poor diets tended to be low. Thus three of the four infants in Group 1 who were given low protein diets were found to have haemoglobin levels of 60% at some time between the fourth and tenth week of life, whereas the levels of the six babies in the same weight group who were given high protein diets all remained above 65%. Similarly, three of the six infants in Group 2 who received the low calorie diets of the preliminary series, had levels of 60% or lower, but among 21 in this weight group who received the higher intakes of the first

TABLE 9
THE AVERAGE HAEMOGLOBIN LEVELS

WEEKS	2		3		4		5		6		7		8		9		10		11		12	
	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases	Haemoglobin	No. of Cases
Group 2 .. .. Birth weight 3·0–3·7¾ lb. ..	140	11	120	8	111	17	93	8	86	14	75	4	72	18	78	1	71	8	73	1	77	13
Group 3 .. .. Birth weight 3·8–3·15¾ lb.	131	22	120	18	106	28	87	10	80	22	79	8	76	12	70	8	74	12	76	6	77	19
Group 4 .. .. Birth weight 4·0–4·7¾ lb. ..	126	22	117	11	103	24	83	3	77	13	95	5	72	14	75	4	73	6	84	4	72	10
Group 5 .. .. Birth weight 4·8–4·15¾ lb. ..	134	15	128	5	111	5			82	8	83	3	88	6	67	3	79	4	81	3	83	5
Groups 2–5	132	70	120	42	106	74	89	21	81	57	83	20	75	44	71	16	73	30	79	14	76	47
Standard Deviation ..	±15		±14		±19		±21		±12		±12		±12		±10		±8		±10		±11	

period and the optimum diet of the second period, 19 maintained levels over 65% and only one baby's level fell to 60% and one other to 62%. It seems evident that nutritional deficiency increases the incidence of low levels amongst babies with birth weights below 3½ lb. Accordingly haemoglobin levels which fall below 65% during the first three months of life should probably be regarded as a sign of anaemia in premature infants, and the cause should be sought. Although a relationship between defects in the diet and low serum protein and haemoglobin levels has been found in our investigation, a much larger series of infants in the lower weight groups must be examined in order to establish the validity of these observations.

Non-Protein Nitrogen Levels. The samples of serum used for the estimation of protein were analysed for non-protein as well as for total nitrogen, and a comparison has been made between the non-protein nitrogen levels of the infants receiving the different diets which were used in the investigation. Only the levels of the infants in Groups 2, 3, and 4 who were between the ages of one and four weeks have been included. The levels from the babies in the three weight groups have been averaged together for each of the diets and Table 10

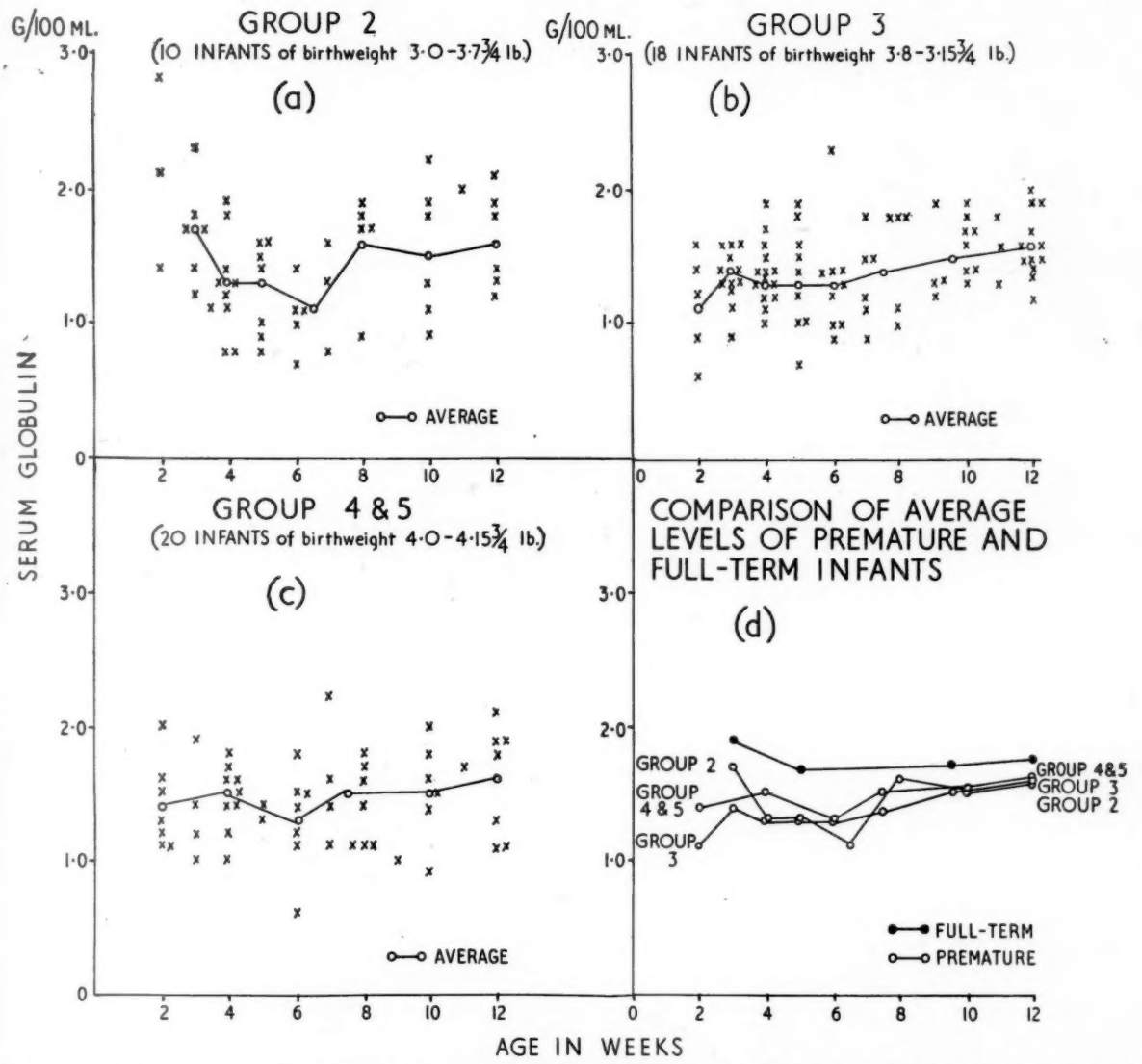

FIG. 6.—6*a*, 6*b*, and 6*c* show the individual and the average globulin levels of the infants in the weight groups 2, 3, and 4+5 respectively. The average levels for these groups are also shown in 6*d* for comparison with each other and with the average levels for full-term infants. The optimum diet was the higher calorie and high protein diet of Period II.

TABLE 10
NON-PROTEIN NITROGEN LEVELS

No. of Levels	Diet	Average Level (mg./100 ml.)	Range (mg./100 ml.)
29	High protein of first period	39	11–57
44	Low protein control of first period	28	16–57
66	Higher calorie, high protein of second period	27	11–41

shows the results. It can be seen that the average non-protein nitrogen level of the infants receiving the higher calorie, high protein diet of the second period was similar to that of the babies receiving the low protein control feed of the first period, but that it was lower than that of the babies on the high protein feed of the first period. This finding suggests that there may have been a protein-sparing effect from the higher calorie diet of the second period. Such an effect would have enabled the infants to utilize a greater amount of the protein in the diet of the second period than could be utilized from the equally high protein diet of the first period.

Discussion

The present investigation has yielded valuable information concerning the nutrition of premature infants. In agreement with previous investigators it has been found that these babies, after an initial loss of weight, may be expected to gain weight at the same rate as the foetus *in utero*, provided that they are given adequate diets. If, however, their diets are inadequate they may gain at a slower rate. Nutritional deficiency should therefore be suspected in babies who gain weight slowly.

The results of this investigation do not allow a definition of the optimum diet for premature infants to be made. The average weight curves and the serum protein and haemoglobin levels of the infants observed in the second period seem to show, however, that their nutritional requirements were being met by the diets which they were receiving. The signs of under-nutrition, i.e. slower gain in weight and relative hypoproteinaemia and anaemia, which occurred in some of the infants of low birth-weight (i.e. below 3½ lb.) observed in the first period, suggest that they were receiving diets which were insufficient. These diets were low in calories and/or protein compared with the theoretical requirements of premature infants. Although not apparent from the methods which have been used for assessing their progress, lesser degrees of under-nutrition may have occurred also in some of the bigger premature infants, who were given similar diets, but for shorter periods. In this connexion attention is drawn to the fact that gain in weight is not a direct index of 'normal' growth, and that the percentage composition of the body with regard to water, minerals, protein, and fat may not be the same in under-nourished babies as it is in the well nourished foetus or young infant.

The slower rate at which weight was gained by the smaller (Group 2) infants who received the high protein diet of the first period compared with the progress of those who received the same protein but higher calorie intakes in the second period (Fig. 1*a*), must not be attributed without question to the difference in their intake of calories. It may have been due to the quality of the preparation ('Ashe') of casein hydrolysate which was used, e.g. its low calcium content might have reduced its growth-promoting properties. It should be noted that the serum protein levels of the infants who were receiving it were within the 'standard' range set by the results obtained from babies observed in the second period of the investigation. If knowledge were available concerning the relative biological efficiency of the two preparations of casein hydrolysate it might help us to interpret our results.

Casein hydrolysate has been found to be well tolerated by premature infants and it is therefore a valuable form of nitrogenous food with which to augment their protein intake. The effects of the diets used in our investigation and of those used by Gordon *et al.* (1947) may suggest that preparations of predigested protein, such as casein hydrolysate, have no advantage over the protein in half-skimmed milk mixtures. The alimentary tolerance of premature infants for whole milk protein might break down, however, if the conditions for nursing them were unlike those at the New York Hospital. There, the temperature and humidity in the premature infant units are accurately controlled and therefore the baby's intake of total fluid can be safely restricted to 150 ml. or less/kg./day. Also, enough skilled nurses are available to give feeds by gavage at three-hourly intervals throughout the 24 hours. The amount of curd in the half-skimmed milk might not be so well tolerated if two-hourly feeds were being used, or if water were being given between feeds at times when the stomach was still partly filled.

It has been suggested that the low excretory function of the kidneys in premature infants restricts the amount of protein and minerals which they can tolerate. The studies of Gordon *et al.* (1947) seem

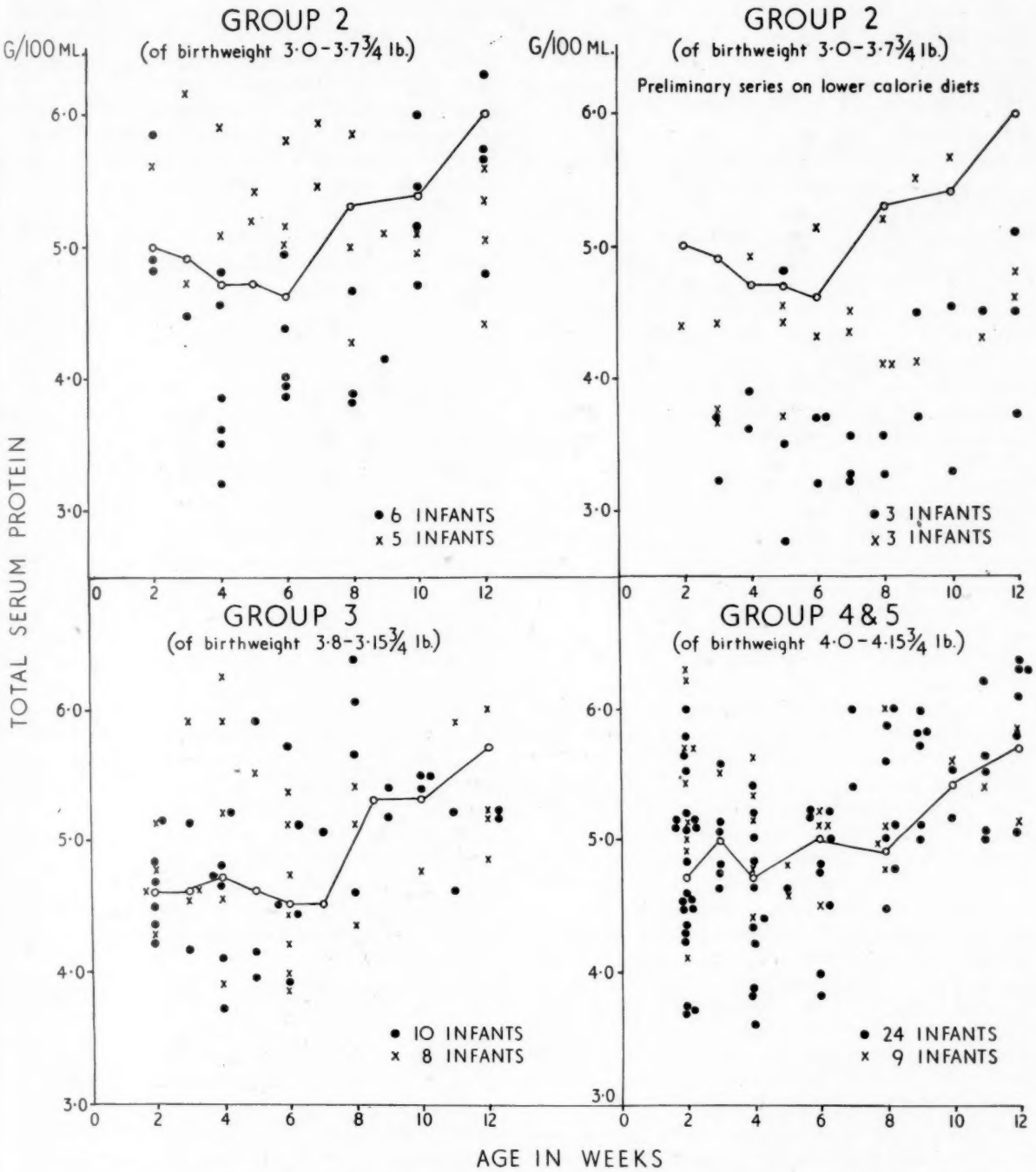

FIG. 7.—The total serum protein levels of the infants receiving the different diets of the first period may be compared with the average levels of the infants receiving the optimum higher calorie and high protein diets of the second period. The infants have been grouped according to their weight at birth as in the previous diagrams, but the levels of the infants in Group 2 who received the low calorie diets of the preliminary series have been recorded separately (Fig. 7*b*). The levels of the infants in the first period have been recorded for those receiving the high protein diets and for those receiving the low protein control diets, while the average levels of the infants receiving the optimum diet of the second period have been recorded o—o.

to show that the excretory load from a diet containing twice as much protein as would be obtained from human milk lies well within the capacity of their kidneys. The range for the non-protein nitrogen levels of the infants in this investigation who were receiving 6·0 g. or more of protein/kg./day provide further evidence that this amount is not excessive.

Some paediatricians are sceptical about rapid early progress in premature infants and maintain that it is due to ' pushing ' food; they believe that a slow gain in the early weeks should be regarded as satisfactory. According to our observations, infants who gain slowly may suffer from some degree of undernutrition at six to twelve weeks of age. Under such circumstances it would seem advisable to give high amounts of protein and minerals in order to make up for previous deficiencies.

Detailed information obtained from the follow-up care and observation of infants during the first year of life has not been presented in this paper. The later progress of the infants who weighed less than 2½ lb. at birth is of particular interest, however, in connexion with the findings relating to their early development. The four infants in this group, each of whom had gained weight very slowly during the first three months of life (Fig. 2*a*), all made very rapid progress at some period before reaching nine months of age, so that their weights then ranged between 14 lb. 12 oz. and 16 lb. 0 oz. This finding is somewhat surprising in the light of observations which have been made on the nutrition of young animals (Wallace, 1944; 1946). The degree of undernutrition which had occurred in these infants during their early weeks of life was evidently not severe enough to have restricted their development (as judged by weight gain) at later ages. Furthermore, clinical examination failed to show that these babies had been reduced to the plane of nutrition, described by McMeekan and Hammond (1940) in sheep, which causes permanent changes in the proportions of the body. The consequences of their undernutrition appear therefore to have been short-lived. Nevertheless, the premature infant who is undernourished must be at a disadvantage while this condition persists, the chief danger, as in all states of debility, being infection.

Although the serum protein levels of the premature infants receiving our optimum higher calorie and high protein diet were low compared with those of full-term infants, these levels are regarded as being ' physiological ' for the early weeks of life. Both the albumin and the globulin levels were low, but the globulin values were relatively lower than the albumin. It would be interesting to study the gamma globulin fraction, and, if low levels were found, they might be related to the high death rate from infection amongst the prematurely born.

The present investigation has yielded observations which lead to tentative conclusions only, but an opportunity to continue these studies is not immediately available. It is hoped that they may provide a useful basis for further work and that they will stimulate a more complete investigation of the nutrition of small premature infants.

Summary

Two hundred and three premature infants were the subjects of an investigation which was planned in the first place as a trial of casein hydrolysate. Two preparations were used and were found to be well tolerated.

The relationship between the diet and the nutrition of the infants was studied by recording their gain in weight and by estimating their serum protein and haemoglobin levels during the early weeks of life.

The average rate of gain in weight (from the third week after birth) by premature infants receiving adequate diets has been found to be the same as that of the foetus *in utero*, and consequently it is proposed that this rate should be regarded as a ' standard ' and slower gains as a sign of undernutrition. The average rate of gain in weight by the bigger infants (birth weight over 3½ lb.), did not vary with the diets which were used in this investigation and was equal to the ' standard.' In contrast, some of the smaller infants (birth weights under 3½ lb.), failed to gain at the ' standard ' rate. They were receiving lower intakes of calories and/or protein than those of similar birth weight who gained at the ' standard ' rate.

The average serum protein levels of the premature infants receiving the optimum diet of the second part of the investigation were found to be lower than those of full-term infants. This difference was due to both lower albumin and lower globulin fractions. Some of the infants with birth weights below 3½ lb. who failed to gain weight at the ' standard ' rate, showed even lower serum protein levels at four to eight weeks of age. These babies were receiving the poor diets to which reference has already been made. Low albumin levels were found in these cases which suggests that under-nutrition was the cause of the hypoproteinaemia.

Severe anaemia was rarely found to be present in the premature infants who were observed in this investigation. Levels below 60% were confined to the groups of infants of low birth weight, who received the relatively poor diets.

Special attention to the nutritional requirements of infants who weigh less than 3½ lb. at birth is clearly indicated. Premature infants, including those of low birth weight, are able to assimilate diets containing at least 120 calories and 6·0 g. protein/kg./day during the early weeks of life. The minimum requirements of food for premature infants cannot be estimated from the knowledge which is at present available. They should therefore be given diets which contain enough protein and minerals to exceed their needs, so that a good nutritional status may be assured throughout the early months of life.

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NEURO-MUSCULAR INCOORDINATION AT THE CARDIA IN THE NEWBORN

BY

JOHN THOMSON, M.D., D.P.H., D.C.H.
From the Department of Child Life and Health, Edinburgh University

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Hurst (1915) coined the word achalasia, i.e. absence of relaxation, to describe a neuro-muscular incoordination in the alimentary tract. Previously, Rolleston (1896) had suggested such an incoordination to explain some cases of dilatation of the oesophagus. The condition was then known as cardiospasm, a word introduced in 1882 by Mikulicz (1904). Earlier it was known as simple or idiopathic dilatation of the oesophagus and had been described by Hannay (1833). While most of the writings on the subject refer to later childhood and maturity, the presence of the condition in infancy has long been recognized. Rotch (1896) described simple dilatation of the oesophagus in a girl who died aged ten weeks. Luschka (1868) recorded what he considered to be congenital dilatation of the oesophagus, and Zenker (1878) reported the appearance of dilatation of the oesophagus above the cardia in a premature infant of seven months gestation, who died at the age of seven days as a result of haemorrhage from the umbilicus.

Recognition of the condition in the neonatal period has been rare, though many of the cases diagnosed at a later age gave a history of vomiting from birth or soon after (Langmead, 1919; Morgan, 1911).

Tyson (1926) was the first to record a case of achalasia in the neonatal period. He called it phrenospasm. Birnberg (1929) published three cases of cardiospasm. Segar and Stoeffler (1930) recorded two cases. Olmsted (1931), Bogert (1933), and Vinson (1945) reported one case each. Aikman (1933) recorded four cases. The main features of these cases, all of which were diagnosed radiologically, are given in Table 1. A case of uncontrollable vomiting from the second day of life onwards and recorded by Garrahan and Muzio (1932) has not been included in this table. There is some doubt about the diagnosis of this case and no supporting radiological evidence appears to have been obtained at the time of the illness. In an extensive search of the literature no cases other than these were found. This relative infrequency with which the condition in the newborn infant has been recorded, is justification for recording the following three cases of neuro-muscular incoordination. The first two cases appear to be typical of achalasia of the cardia, but the third case is different and requires separate discussion.

Case Reports

Case No. 1. Baby O'H., born on January 4, 1949, was a full-time female infant weighing 7 lb. 15½ oz. at birth. She was the result of a second pregnancy; the parents were unrelated. A twenty-two-hour labour was terminated successfully in a difficult delivery with Kielland's forceps. The infant was in poor condition, but revived satisfactorily under treatment, which included lobeline 1 ml. and 'synkavit' 1 ml., both given intramuscularly, and continuous oxygen therapy. As a prophylactic measure an initial dose of 30,000 units of penicillin was given intramuscularly and followed by doses of 10,000 units at three-hour intervals until 190,000 units had been given.

Feeding was begun with a 7% solution of lactose water. This was taken well. On the second day no clinical signs of cerebral trauma were observed but the infant vomited once a little brownish, blood-stained mucus. Meconium was passed normally. On the third day vomiting during and immediately after feeding became troublesome. It was not forceful. Gastric lavage was carried out. For this purpose a soft rubber catheter was passed into the stomach. In doing this, no obstruction was felt and no difficulty was experienced. Improvement of short duration followed the gastric lavage, which was repeated on the fourth day. On that day expressed breast milk was added to the diet. On the fifth day, following a short period of improvement, vomiting during and following feeding recurred. The vomiting was not forceful or projectile. Dehydration became more obvious. The temperature rose to 101° F. The infant continued to feed eagerly but would regurgitate the complete feed unaltered within two minutes of taking it. There was no dysphagia. Ordinary clinical examination showed no cause for the

TABLE 1. DATA OF RECORDED CASES OF NEONATAL ACHALASIA OF CARDIA DIAGNOSED RADIOLOGICALLY

Author	Sex	Birth weight lb.	Birth weight oz.	Percentage Birth weight Lost	Pyrexia	Emesis Began Day	Emesis Character	Atropine and its Derivatives	Gavage	Continuous Dilatation by Catheter	Concurrent Condition	Notes
Tyson, 1926	M.	7	13	12	+	2	R. and P.	+	–	–	Pyloric spasm	Caesarean section. Gastric peristalsis seen. At 33 days, weight 9 lb. No vomiting.
Birnberg, 1929	M.	5	15½	16	+	1	R. and P.	–	+	–	—	Spontaneous delivery. At 8 days on radiograph, no oesophageal stasis, some pyloric stasis had developed. Vomits: 1 or 2 daily till weaned at 9 months.
	M.	7	4	14¾	+	1	P.	–	+	–	—	Spontaneous delivery. At 13 days radiograph negative.
	F.	4	6½	?	–	1	P.	–	+	–	Cerebral haemorrhage	Forceps delivery. Died on fourth day. No necropsy.
Segar and Stoeffler, 1930	F.	7	4	8½	–	4	R.	+	–	–	—	Spontaneous delivery. At 7 days no vomiting. At 14 days birth weight regained. At 1 year and 3 months radiograph of oesophagus negative.
	M.	7	12	14½	–	3	R.	+	+	–	—	Forceps delivery. At 15 days radiograph of oesophagus negative. Weight 7 lb. 6½ oz. No vomiting. At 6 months is over the expected weight.
Olmsted, 1931	F.	?		?	?	1	P.	+	+	–	—	Diagnosed as intestinal obstruction and operated on at 6 days. No abnormality found. X-ray diagnosis made at 5 weeks. Gavage begun. No vomiting after 7 days' treatment.
Aikman, 1933	M.	7	8	16¾	?	1	R.	+	+	2 days	—	At 1 year and 3 months, radiograph positive.
	F.	7	8	?	?	2	R. and P.	+	+	4 days	—	At 15 days, radiograph negative; weight, 7 lb. 12 oz. At 7½ months, 21 lb. 6 oz.
	M.	7	8	?	?	1	?	+	+	18 hours	—	At 14 days no vomiting. Died at 9 months. Necropsy, cardia normal. Oesophagus, slight dilatation. A thymic death.
	F.	8	0	12½	?	2	R. and P.	+	+	–	Pyloric Stenosis	No visible peristalsis. No palpable tumour on x-ray: delay at pylorus. Rammstedt operation at 8 days.
Bogert, 1933	F.	9	8	25	+	1	P.	–	–	2 days	—	At 5 months weighed 11½ lb. Regurgitation still present.
Vinson, 1945	M.	?		?	?	1	?	+	–	–	—	Atropine and nembutal not helpful. At 3 years radiograph of oesophagus negative.

R.=Regurgitation. P.=Projectile.

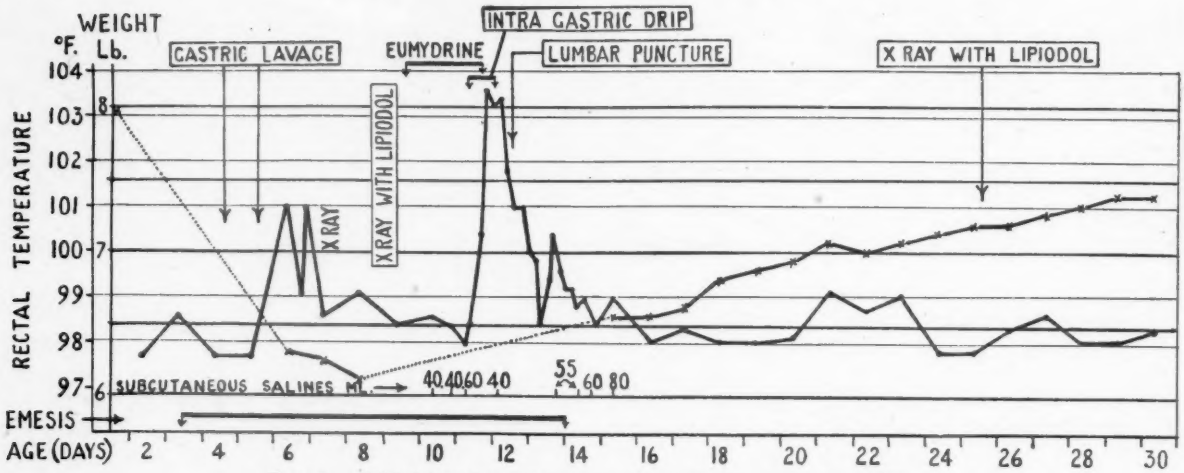

FIG. 1.—Weight and temperature chart of Case 1 (Baby O'H).

vomiting and radiological examination of the thorax was negative. Loss of weight had become marked, so that by the seventh day a loss of 23% of the birth weight had occurred (Fig. 1).

After giving 10 ml. of lipiodol, radiological examination was repeated (Fig. 2). This revealed narrowing at the lower end of the oesophagus which was dilated in its upper and middle thirds. A catheter was passed into the stomach (Fig. 3). This demonstrated the absence of an organic obstruction and allowed the lipiodol to enter the stomach which emptied rapidly. The bulk of the lipiodol was in the small bowel within 15 minutes.

In an effort to overcome this functional obstruction, 'eumydrin' was given in 0·5 mg. doses before food, and routine feeding by gavage was begun. Subcutaneous salines were also given. Towards the end of the tenth day the vomiting became more projectile and a continuous intragastric drip was substituted for gavage. The infant did not tolerate the drip well and vomited the tube once. Following the occurrence of two cyanotic attacks the drip was removed. It had been used for approximately 15 hours. At the same time intolerance to 'eumydrin' developed. The first signs were restlessness and alertness. These were followed by pyrexia (Fig. 1) and later some stiffness of the neck

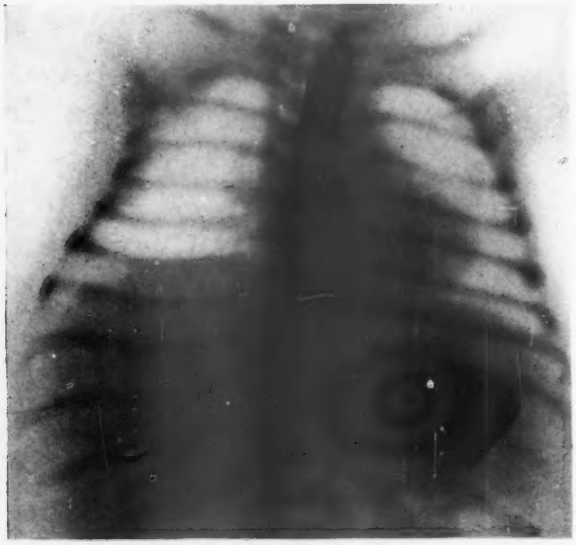

FIG. 2.—Radiograph with lipiodol of Case 1. Anterior view showing dilatation of oesophagus in upper two-thirds and partial obstruction in the lower third.

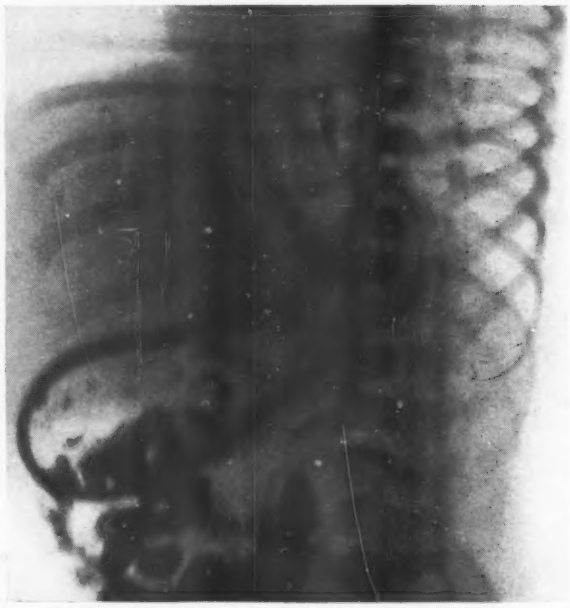

FIG. 3.—Lateral view of Case 1 with catheter in oesophagus and stomach. Note the persistence of the oesophageal dilatation when oesophagus is practically empty.

FIG. 4.—Radiograph (lateral view) with lipiodol of Case 1. Shows absence of oesophageal obstruction and outlines the distal end of the oesophagus.

muscles. The 'eumydrin' was discontinued. A lumbar puncture demonstrated a clear cerebrospinal fluid, not under pressure, and sterile on culture.

Gavage was continued for 18 hours following the removal of the intragastric drip. Thereafter ordinary bottle feeding was begun. At intervals of two hours, 1½ oz. of 1/12 dilution of sweetened condensed milk was given. The infant fed well and was fed slowly. Of the first ten feeds thus given, one was entirely vomited, about ½ oz. of another was returned, and a mouthful of all the others except one, which was entirely retained. The amount and strength of the feeds were increased slowly, but no further vomiting of any note occurred. Subcutaneous salines were discontinued on the fourteenth day. Following a negative radiological examination (Fig. 4) on the twenty-fourth day, feeding at three-hour intervals was begun. The infant was discharged when 36 days old. She weighed 7 lb. 8½ oz. She was then taking a 4-oz. feed in average time. There was no vomiting. She weighed 10 lb. when 11 weeks old.

Case No. 2. Baby C. was a full-time, spontaneously delivered female infant who weighed 6 lb. 3 oz. when born on Sept. 13, 1946. She was an illegitimate child of unrelated parentage. Her condition at birth was good. The passage of meconium was normal. On the second day she began to vomit. The vomiting occurred during and immediately after feeding. It was not forceful. The vomitus consisted of brownish mucoid material

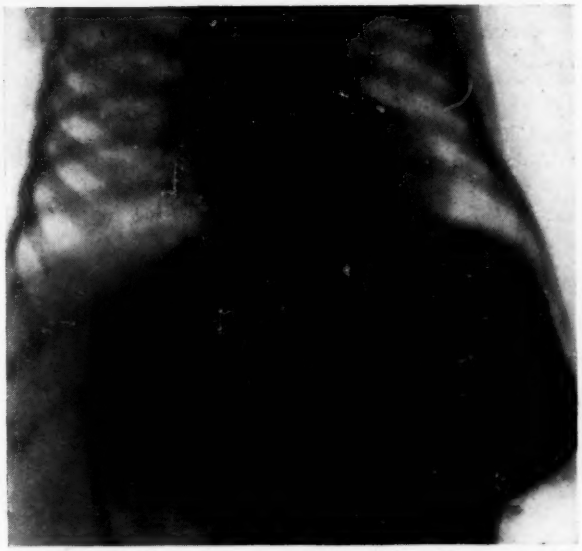

FIG. 5.—Partial side view of Case 2. Compare with Fig. 2.

mixed with milk, but by the end of the third day unaltered food only was returned. Gastric lavage was carried out on the third and fifth days. A soft rubber catheter was used for this purpose and no difficulty was encountered in passing it. The

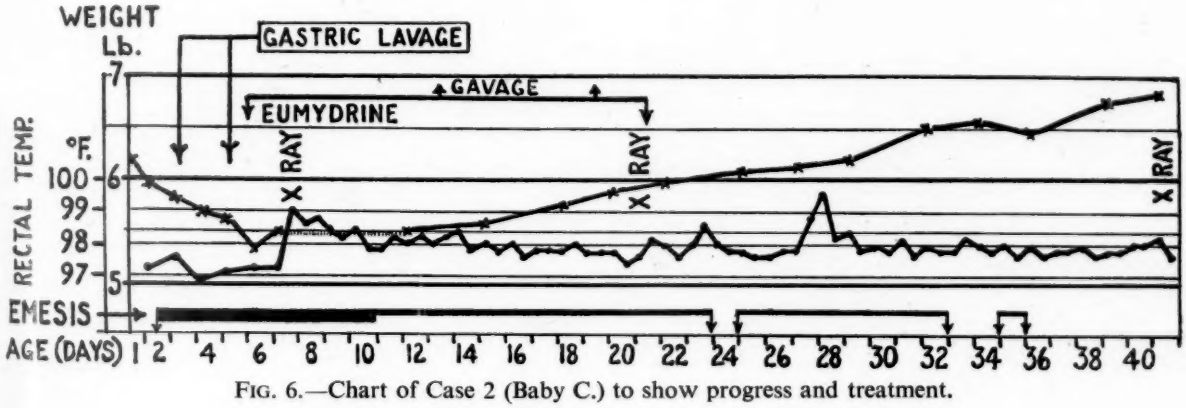

FIG. 6.—Chart of Case 2 (Baby C.) to show progress and treatment.

gastric lavage did not appear to lessen the incidence of the vomiting.

On the sixth day the vomiting became more forceful in character. Medication with 'eumydrin', 0·5 mg. before food, was begun. Next day radiological examination with barium disclosed a dilated oesophagus with some functional delay at the cardia. Some food did pass into the stomach but was again delayed at the pylorus. No gastric peristalsis was seen and no pyloric tumour was felt (Fig. 5). The infant was now fed on a 1/10 mixture of a sweetened condensed milk which was thickened by the addition of a predigested food. The feed was given slowly and when it was finished the infant was laid on the right side. The feeds were taken eagerly and there was little evidence of dehydration. The lowest recorded weight showed a loss of only 9·5% of the birth weight (Fig. 6). By the tenth day the incidence of the vomiting had diminished somewhat and an occasional whole feed was retained. Four or five vomits a day would occur and two of these would be projectile. The projectile vomits occurred up to one hour after the feed had been given.

The infant did no more than hold her own during the first week of 'eumydrin' medication. Accordingly, gavage was begun on the thirteenth day and continued for one week. This resulted in a diminution of the number of vomits, which became regurgitant in character, and 'eumydrin' was stopped on the twenty-second day. The infant continued to make satisfactory progress though regurgitation did not cease until it was five weeks old. A minor respiratory infection on the twenty-seventh day was successfully treated with oral penicillin.

When six weeks old the infant was discharged to a convalescent home, where after a stay of three weeks, she was removed to a nursery. At 11 weeks old she was returned to hospital suffering from conjunctivitis. When seen as an out-patient on this occasion a rather projectile vomit was observed. In view of her past history the infant was kept under observation in hospital for three weeks. A barium series done at this time showed no abnormality of the oesophagus and that there was a very slight residuum in the stomach two and a half hours after the barium was given. The infant was discharged aged 14 weeks. The following week the infant was found buried. She had met a violent death, said to be by drowning. Necropsy disclosed no organic obstruction at the cardia or at the pylorus.

Case No. 3. The mother of this infant, Baby L.A., who was born on Dec. 2, 1942, suffered from syphilis. She had an aortic lesion. Her blood Wassermann reaction had been negative for over 12 months before the birth. Anti-syphilitic treatment had been difficult because of intolerance to arsenic, bismuth, and mercury. This was a first pregnancy. The child was full-time but weighed only 5 lb. 9½ oz. and was 18 in. long. The delivery was instrumental owing to maternal and foetal distress.

Following delivery the infant was not in good condition, and four hours later there was a transient but severe cyanotic attack. Respirations were shallow. Some alertness of the facies developed and a little eye-rolling was observed. Vomiting began on the day of delivery. All these signs were considered to be cerebral in origin and the infant was treated accordingly. She was kept quiet, shaded from light, the minimum of handling was permitted, and she was not lifted to be weighed. Chloral hydrate was given. Meconium was passed normally.

Apart from the vomiting all the signs of cerebral irritation disappeared rapidly. The infant fed well and eagerly but continued to vomit. The vomiting occurred 15 minutes after a feed had been finished; it did not occur during a feed. The feed consisted of 1½ oz. lactose water and 1 oz. breast milk. It was not recorded whether the vomitus contained altered milk or gastric secretion. The infant visibly lost weight and gradually assumed a marasmic appearance. The maximum recorded loss of weight was at 15 days, by which time 22% of the birth weight had been lost (Fig. 7). On the thirteenth day a lumbar puncture disclosed a clear cerebrospinal fluid not under pressure, and intracranial trauma was dismissed as a cause of the vomiting.

The infant was examined radiologically when

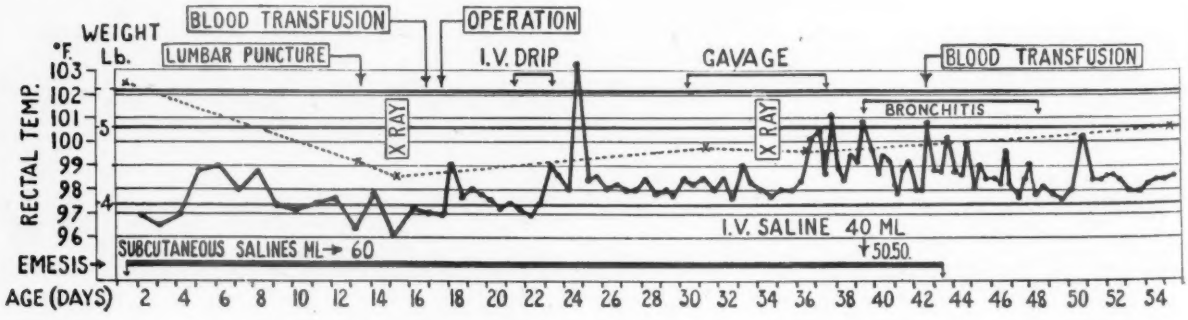

FIG. 7.—Chart of Case 3 (Baby L.A.) to show progress and treatment.

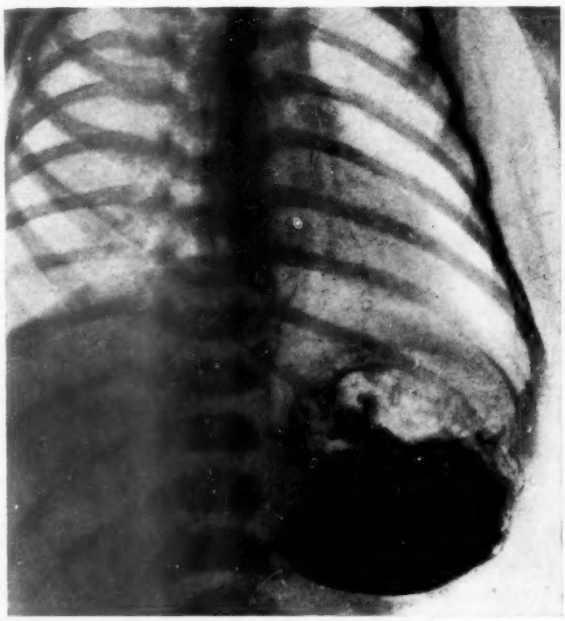

FIG. 8.—Radiograph of Case 3. Barium has gravitated to the pyloric end of the stomach, and oesophageal contents can be seen streaming across the air-filled cardiac end of the stomach. Compare with Fig. 2 (Case 1).

15 days old. The radiologist reported that 'after 90 minutes there is still some barium in the oesophagus and it is present in all films. This would suggest a partial obstruction in the lower third. Barium has entered the small intestine' (Figs. 8, 9, and 10).

Because of the infant's critical condition she was transferred to a surgical ward, and following preparation which included a blood transfusion, gastrostomy was performed on the seventeenth day. A number eight rubber catheter was stitched into the stomach. Through this catheter the stomach was washed out with normal saline and 2 dr. (7 c.cm.) of saline left in. There was a small post-operation vomit. The gastrostomy catheter was used for feeding and during the 48 hours following the operation feeds of 2 dr. (7 c.cm.) in amount were given. At first, sterile water was used and later saline feeds were alternated with feeds of glucose water. The vomiting continued but was less in amount and frequency. The quantity of the feeds was gradually increased, a 50% milk and water mixture being given. With the larger feeds there was an increase in the vomiting and the condition of the infant deteriorated. The progress notes describe the infant as being 'almost moribund'. Although some convulsive seizures appeared, the condition of the infant improved steadily following an intravenous drip of glucose saline which was set up on the twenty-first day, four days after gastrostomy. Fifteen ounces of glucose saline were given in 36 hours. The cause of the seizures was not determined.

Gavage feeding was begun 13 days after gastrostomy. On the same day the case notes state, 'A no. 10 catheter was passed down the oesophagus. Great difficulty was experienced when the tip reached the lower end of the oesophagus. The catheter was passed twice daily thereafter, with increasing ease each time'. After five days of gavage, a second radiological examination was made. The radiologist reported 'no obstruction or abnormality of the oesophagus on swallowing barium. No retention in the oesophagus, but a slight tendency to regurgitation. Some delay in emptying from the stomach—up to 20 hours—but no hold-up in small or large intestine'. Within 48 hours of the radiological examination the infant became febrile, and later a well-marked bronchitis was apparent. (In considering this phase of the illness, the possible inhalation of barium must be kept in mind.) The condition of the infant again deteriorated. Hypodermoclysis and venoclysis were necessary and finally a blood transfusion was given.

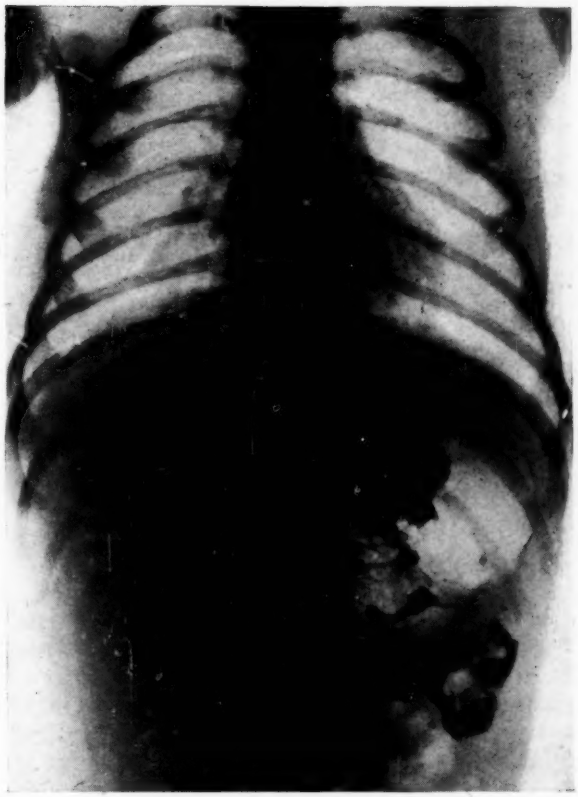

FIG. 9.—Radiograph taken 35 minutes after Fig. 8. Shows an increase in the amount of barium in the oesophagus compared with Fig. 8. There is free passage of barium into the small bowel. Note the irregular outline of the lower end of the oesophagus compared with Figs. 2 and 5.

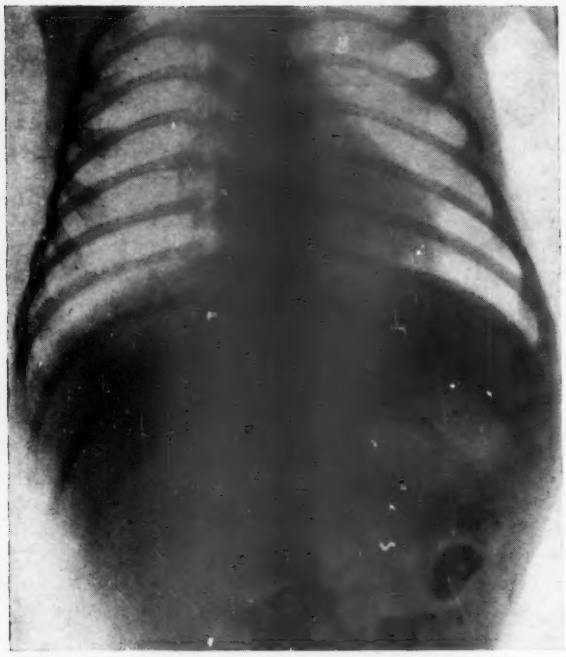

FIG. 10.—Radiograph taken 80 minutes after Fig. 8. Note the presence of regurgitated barium in the oesophagus.

The temperature subsided gradually and about the same time the vomiting ceased. She was discharged from hospital when eight weeks old and weighed 5 lb. The gastrostomy tube was removed, but the date on which this was done is not given in the case notes.

The infant's subsequent history shows that at 16 weeks and 29 weeks she weighed 9 lb. and 14 lb. respectively. The gastrostomy wound was entirely healed at 16 weeks. At 14 months she was thought to be backward, and at 21 months she was referred to the clinic for mentally defective children. There she was classified as microcephalic. She was last seen at that clinic when 3 years, 3 months old.

Discussion

Reference to Table 1 shows that achalasia of the cardia in the newborn infant has been found in both sexes and in full-time and immature infants. The presenting sign is vomiting. The day on which this sign appears is variable, as is the character of the vomiting. Factors other than the presence of neuro-muscular incoordination or sympathetic-parasympathetic imbalance may account for this. In Case 1 vomiting did not begin until the third day. It is probable that the oesophagus could contain the relatively small and infrequent feeds of 15 ml. of 7% lactose water, which were given. Had the feeds been larger vomiting might have begun sooner, as it did in Case 2, or on the first day, as has been recorded in seven of the cases in Table 1.

In some instances vomiting becomes more projectile in character. This change was present in four of the recorded cases. The development of pyloric spasm is the reason given in the cases recorded by Tyson (1926), Birnberg (1929), and in my Case 2. In one of Aikman's cases pyloric stenosis was certainly the cause. The remaining one of the four cases referred to was recorded by Aikman, and it resembles Case 1 in that no definite cause can be given for the projectile vomiting, other than oesophageal peristalsis.

It is notable that in four cases only projectile vomiting has been recorded. Cerebral haemorrhage may have been the explanation in one of Birnberg's cases. It is unfortunate that no necropsy was performed on this infant, who died on the fourth day of life. In Olmsted's case, vomiting was sufficiently impressive to give rise to a diagnosis of intestinal obstruction. At operation no obstruction and no cause for the vomiting was found. The vomiting continued after the operation. No explanation of the projectile vomiting was given in the two remaining cases. In three of the recorded cases only regurgitation was observed.

The vomiting occurs during or immediately after feeding. This is not a diagnostic point of great differential importance, since vomiting at this time may also occur in pyloric spasm, pyloric stenosis, complete gastric spasm (Lust, 1925), and in cases of excessive relaxation of the cardia (Neuhauser and Berenberg, 1947). The vomitus in an uncomplicated case of achalasia of the cardia consists of unaltered food. This is not so if either pyloric spasm, pyloric stenosis, or gastric spasm is concurrent. Thus the character of the vomitus is not always a reliable diagnostic point.

In the last resort the diagnosis of achalasia of the cardia depends upon radiological examination. For this purpose lipiodol should be used in preference to barium which was used in all cases recorded so far. The risk of a fatal pneumonia following the inhalation of regurgitated barium ought not to be taken. The first impression one obtains from an inspection of Fig. 2 is that the gap between the lower end of the dilatation of the oesophagus on the one hand, and the gastric shadow on the other, is rather more than one expects to find in achalasia of the cardia. This is accounted for by the relatively greater length of the cardiac portion of the oesophagus in the newborn infant (Hurst, 1925). The unobstructed passage of a catheter into the stomach can also be demonstrated radiologically. This was done in Case 1 (Fig. 3).

Apart from vomiting, the outstanding feature of achalasia of the cardia in the newborn infant is progressive loss of weight. Exceptionally, this may be severe. In six of the recorded cases it was of the order of 15% of the birth weight. A loss of 8·5% in one case and 25% in another represent the extreme of loss of weight which have been recorded. No record of the loss of weight has been given in five of the cases. In Case 2 the loss of weight was relatively low at 9·5% of the birth weight, but, in Case 1, 23% of the birth weight was lost. This large loss of weight is exceeded by the case of Garrahan and Muzio (1932) who recorded a loss of 47% of the birth weight over a period of 18 days in an infant who weighed 3,000 g. (6 lb. 10 oz.) and who recovered. It is to be noted that this infant was born of syphilitic parents and that it had a salvarsan dermatitis.

In the treatment of achalasia of the cardia atropine has been used by five observers (nine cases). No general agreement concerning its efficacy has been expressed and Vinson stated that it was not helpful. In the present instance the 'eumydrin' which was given was not tolerated by Case 1, but seems to have been beneficial in Case 2. Gavage was used by four of the observers (nine cases), but only three observers used gavage and atropine in the same case (six cases). Case 2 was treated in this manner. Continuous dilatation of the cardia by leaving a soft rubber catheter in position was practised by two authors (four cases). In three of Aikman's cases this treatment was combined with atropine and gavage before and after the period of continuous dilatation. In Case 1 this procedure was also followed.

The prognosis of achalasia of the cardia in the neonatal period is good. The two deaths which have been recorded were not attributable to achalasia of the cardia. In two cases regurgitation of lesser degree continued till nine months and five months respectively. The latter of these two cases was only 2 lb. over its birth weight when it was five months old (Bogert, 1933). One case with a positive radiograph at 15 months is reported by Aikman. In the present instances a cure appears to have been obtained, as in the remaining eight recorded cases. The death of Case 2 was attributable to violence, and the necropsy produced no evidence of an obstructive lesion.

First consideration of the history of Case 3 gives the impression that an oesophageal obstruction was the cause of the vomiting. The first *x*-ray report 'suggests' that there is an oesophageal obstruction, and the surgeon's report of 'great difficulty' in passing a catheter through the lower end of the oesophagus is supporting evidence. It is difficult to correlate these findings with vomiting following feeds given by gastrostomy tube. The idea is engendered that there may have been no oesophageal obstruction, but rather a pyloric one.

Inspection of the *x*-ray photographs upon which the first *x*-ray report is based is of considerable interest. After giving barium, three photographs were taken in rapid succession. The third of these is reproduced (Fig. 8). It shows a relatively small stomach which has very free communication with the oesophagus. There is an excellent demonstration of the oesophageal contents streaming across the air-filled cardiac end of the stomach towards the pyloric end, to which the barium meal has already gravitated. A further photograph taken 35 minutes later shows that some barium has passed into the small bowel, and that there is a considerable amount of barium in the oesophagus (Fig. 9). This has been interpreted as delay in emptying the oesophagus.

Comparison of Fig. 8 with Fig. 9 shows without doubt that there is less barium in the oesophagus in the first of these two photographs. No additional barium had been given. Regurgitation from the stomach is the only means by which the appearance seen in the later photograph can be explained. It may be that there is some pyloric spasm present. Another photograph taken 90 minutes after administration of barium shows some barium still in the oesophagus (Fig. 10). This interpretation of the first series of *x*-ray photographs is similar to the report given on the second series.

The infant was fed by gavage for four days before the taking of the second series of photographs. No difficulty was experienced with gavage so that the tube used cannot be considered to have dilated a stricture. Also before the second series of photographs a number ten catheter was passed into the stomach twice a day, eight times in all. This was done blindly. 'Great difficulty' was experienced on the first occasion, but it was passed 'with increasing ease each time'. Since vomiting persisted after this treatment it may be doubted whether any pre-existing stricture was dilated.

In reviewing the diagnosis of this case one may consider whether excessive relaxation of the cardia, perhaps accompanied by pyloric stasis or spasm, might account for the illness. Hitherto, excessive vomiting because of an undue relaxation of the cardia has not been stressed as a serious pathological state in the newborn. It has been recorded in an adult (Berk, 1945). The only reference to the condition in the newborn is that of Neuhauser and

Berenberg (1947). In routine radiological examinations of 2,000 vomiting newborn infants, these authors found 12 infants who showed marked relaxation of the cardia. In some of these cases, inspiration, crying, and coughing was sufficient to flood the oesophagus with gastric contents. In others the lightest of pressure upon the abdomen produced the same result. This regurgitation sometimes stimulated a gag reflex which resulted in true vomiting. They found that the vomiting usually started in the first few days of life, became progressively worse, and soon occurred with every feed. The vomiting might take place during a feed, but was most apt to occur after the infant was put back in his cot. It is to be noted that the vomiting in Case 3 occurred a quarter of an hour after the feed was finished. The authors treated their worst cases by keeping them in a semi-sitting position day and night, and using a thickened feed. There were no concomitant abnormalities in any of their cases, and it must be noted that none of these patients presented the picture of severe wasting such as was seen in Case 3. They seem to have responded to the simple nursing technique instituted, but Case 3 was not so treated.

The presence of pyloric spasm in Case 3 is suggested by the second *x*-ray report which states that ' there was some delay in emptying from the stomach up to 20 hours '. Before assessing the value of this report, it is essential to know how long it takes the normal newborn infant to empty the stomach. On this point there is surprisingly little authoritative information. In an extensive radiological study made by Henderson (1942) it was shown that the stomach was completely empty at the end of eight hours in 30 (27·27%) out of 110 normal newborn infants, and that 40 (36·36 %) infants had some barium remaining in the stomach at the end of 24 hours. This suggests that great care should be taken in interpreting a failure to empty the stomach at 20 hours as a delay. It would appear that in Case 3 there may have been no undue pyloric delay and that excessive relaxation of the cardia with an easily stimulated gag reflex may be an explanation of the illness.

Summary

Two cases of achalasia of the cardia in the newborn infant are reported.

The literature on achalasia of the cardia in the newborn is reviewed.

A case of vomiting of doubtful origin in the newborn infant is described.

Consideration is given to a diagnosis of excessive relaxation of the cardia, achalasia.

It gives me pleasure to acknowledge access to the hospital record of Case 3 which was in the care of Dr. J. L. Henderson and Miss G. Herzfeld.

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HAEMOLYTIC DISEASE OF THE NEWBORN*

PART I: A CLINICAL-PATHOLOGICAL STUDY OF 157 CASES

BY

ALBERT CLAIREAUX, M.D., M.R.C.P.(Edin.)
From the Department of Child Life and Health, University of Edinburgh

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Since the discovery of the Rh blood groups (Landsteiner and Weiner, 1940) many articles on the subject of haemolytic disease of the newborn have been written. Gilmour (1944) in this country and Potter (1944; 1946) in America have presented authoritative accounts of the pathology of haemolytic disease, but, as the former points out, this aspect of the condition has received far less attention than it has merited.

Present Investigation

The clinical records of all cases of haemolytic disease in the Simpson Memorial Maternity Pavilion, Edinburgh, the Royal Hospital for Sick Children, Edinburgh, and the Elsie Inglis Memorial Maternity Hospital, Edinburgh, in the period 1937-47 have been studied. Also all necropsy material from fatal cases has been examined in detail. The serological investigation of the Rh blood groups in affected families was carried out at the clinical laboratories of the Royal Infirmary, Edinburgh. It must be emphasized, however, that most of the cases in this series occurred before serological Rh testing of mothers and their affected offspring had become a routine antenatal procedure.

Analysis of Cases

The total number of patients was 157, the offspring of 149 women.

Sex. Eighty were male and 67 were female. In ten cases no record was available. The slight preponderance of males over females has probably no statistical significance.

Maturity. One hundred and eleven infants were mature and 39 were premature. Prematurity does not appear to play a conspicuous part in the aetiology but it does add to the hazards of affected infants.

Twin Pregnancies. The disease occurred in six sets of twins and in four of these sets both twins were affected. One pair were examples of hydrops foetalis; two pairs were cases of icterus gravis neonatorum with kernicterus. In the fourth pair, one twin exhibited icterus gravis neonatorum while the other was an example of hydrops foetalis. In the remaining two sets, the first twin was spared while the other was affected by icterus gravis and kernicterus. This indicates that each twin may not necessarily suffer to the same extent, although exposed to the same concentration of maternal antibody. When one twin escapes altogether the father is usually heterozygous (Rh rh), one twin is Rh positive and affected, while the other is Rh negative and escapes.

Obstetrical Histories of the Mothers. A full history of previous pregnancies, miscarriages, and abortions was obtained from 128 of the 149 women. These 128 women gave birth to 478 infants and foetuses, and had borne a total of 278 infants and foetuses before a case of haemolytic disease was diagnosed among their offspring. Of 278 early pregnancies, 37 ended in miscarriages and 23 in stillbirths. Of the remainder, 14 infants died in the neonatal period. Thus only 204 pregnancies resulted in the birth of normal, healthy children. The number of unsuccessful pregnancies, 60 out of 278 (21·5%), is considerably above that in an unselected series (11% according to Potter, 1948). In this series 10 of the 149 women (7%) were pregnant for the first time. The results are shown in Table 1.

Table 1
Results of First Pregnancy in Ten Women

Type of Haemolytic Disease	No.
Hydrops foetalis	3
Icterus gravis and kernicterus (died)	2
Icterus gravis neonatorum (died)	3
" " " (recovered)	1
Haemolytic anaemia	1
Total	10

A history of previous blood transfusion or of intramuscular injections of blood was not obtained from these ten women.

* Part of a thesis presented for the degree of Doctor of Medicine of the University of Edinburgh.

A further five women (3·5%) had had previous pregnancies ending in miscarriages and had no viable children before the first child with haemolytic disease was born (Table 2). One of these women had after a miscarriage been transfused with blood not tested for Rh compatibility.

TABLE 2
RESULTS OF FIRST PREGNANCY IN FIVE SUBJECTS PREVIOUSLY TRANSFUSED

Type of Haemolytic Disease	No. of Cases
Hydrops foetalis	2
Icterus gravis and kernicterus (died) ..	2
Icterus gravis (recovered)	1
Total	5

It will be seen that the type of haemolytic disease in these early pregnancies is generally severe. This is not in accordance with the findings of Potter (1948) and other workers.

Twelve women had had one or more miscarriages between the birth of the last normal child and the first suffering from haemolytic disease. In three instances these miscarriages had led to severe haemorrhage which had been treated by blood transfusion, when the donor blood was not tested for Rh compatibility. These cases serve to emphasize that incompatible blood transfusion is more effective than pregnancy in sensitizing the mother and that the disease is liable to take a severe form in the results of a pregnancy following such a transfusion.

It will be seen from Table 3 that 66% of the women gave birth to their first affected child before their fourth pregnancy. Of the 129 affected children, 90 died or were stillborn, a mortality of 70%.

In this series 33 women had one or more pregnancies after the birth of a child with haemolytic disease. (Two of these later pregnancies ended in miscarriage.) These 33 women had a total of 70 children, of whom 68 were affected by haemolytic disease. Of the 68 children, 35 were stillborn, 13 died, and 20 were affected but survived. The survival rate of 30% is similar to that of first affected infants. Potter (1948) found a survival rate of only 10% among offspring of later pregnancies.

The 128 women in my series thus gave birth to 197 children affected by haemolytic disease. Of these, 59 survived, 79 died, and 59 were stillborn, a mortality of 70%.

Abnormalities in Pregnancy and Delivery. The majority of the women had uneventful pregnancies. Sixteen women (11%), however, had some disturbance of pregnancy. Their offspring showed 100% mortality. Six were stillborn and the remainder died after birth. The results of these pregnancies is shown in Table 4. In nine cases the delivery was not spontaneous. Three infants were delivered by forceps, two died, and one recovered. Two infants were delivered by caesarean section, one died and one recovered. Three cases were breech deliveries and all died. One was an assisted breech delivery and recovered.

TABLE 3
FIRST PREGNANCY IN WHICH HAEMOLYTIC DISEASE WAS DIAGNOSED

Results	No. of Pregnancy										Total
	1	2	3	4	5	6	7	8	9	10	
Infant survived	4	13	11	5	2	2	1	0	0	1	39
Infant died	6	24	16	6	9	0	3	1	1 (B.T.)	0	66
Stillbirth	3	3	7	4	2	5	0	0	0	0	24
Total	13	40	34	15	13	7	4	1	1	1	219*

* 1 pair of twins is included in this table. B.T. Case following transfusion in blood not tested for Rh compatability.

Investigation of Rh Blood Groups. Serological investigations were carried out on 56 cases. In 50 cases (90%) the usual serological pattern of

TABLE 4
RESULTS OF ABNORMAL PREGNANCIES IN 16 WOMEN

Complication	Result in Foetus		
	Still-born	Died	Total
Hydramnios	3	–	3
Eclampsia	1	–	1
Pre-eclamptic toxaemia ..	2	4	6
Secondary syphilis ..	1	–	1
Antepartum haemorrhage	–	3	3
Hypertension	–	1	1
Cardiac disease	–	1	1
Total	7	9	16

Rh negative mother and Rh positive father and child was present. In five out of the six remaining cases the mother and child were both Rh positive. In one case, the mother was Group 0 Rh negative and the child was Group B Rh negative. The mother's blood was tested for the presence of agglutinins in 13 instances.

Lack of sera prevented the full genotyping of the fathers of affected children, and so the number of results obtained in this series is too small to allow of comment.

Previous Blood Transfusion in the Mother. In three cases, Rh negative women had been treated by blood transfusion of unspecified blood after a miscarriage. The following pregnancy the women were delivered of infants suffering from icterus gravis neonatorum. Two of these infants recovered but one developed kernicterus and died.

Clinical Features of Affected Cases. Haemolytic disease in the foetus or infant usually takes the form of hydrops foetalis, icterus gravis neonatorum, or haemolytic anaemia. This classification is not rigid and some foetuses with hydrops may be slightly jaundiced, and some of the patients in this series with icterus were oedematous. For the purpose of this survey the 157 patients have been classified according to the type of disease they most closely resembled (Table 5).

TABLE 5
ANALYSIS OF TYPES OF HAEMOLYTIC DISEASE IN 157 CASES

	Live Infants	Stillborn Infants		
		Un-Macerated	Macerated	Total
Hydrops foetalis	5	21	10	36
Icterus gravis neonatorum	110	—	—	110
Haemolytic anaemia	11	—	—	11
Total	126	21	10	157

It will be seen that icterus gravis neonatorum is the most common and haemolytic anaemia the least common manifestation of the disease. This is in accordance with the findings of most workers. It is probable that a number of cases of both haemolytic anaemia and icterus gravis occurring during the earlier period of this survey were not diagnosed as they were clinically mild and serological tests were not available.

HYDROPS FOETALIS. From a study of Table 5 it will be seen that the foetus is usually stillborn (31 cases) and frequently macerated (10 cases). Less commonly a live birth occurs (5 cases), but death usually follows in a matter of hours. As the name implies, there is generalized subcutaneous oedema, the abdomen is distended with fluid, and the skin is pale or macerated. The degree of anaemia is severe. Jaundice is not the rule, but the umbilical cord may be yellow in colour (Fig. 1).

ICTERUS GRAVIS NEONATORUM. Jaundice is the salient feature of this type, and until recently, might be said to be the only constant feature. Modern serological tests, however, have altered the picture. The jaundice may be present at birth, in which case the vernix caseosa may be golden yellow in colour, or the jaundice may appear within the first 24 hours. It is infrequently delayed beyond 48 hours (Table 6).

TABLE 6
TIME OF ONSET OF JAUNDICE

Time	No. of Cases
At birth	32
Under 24 hours	55
24-48 hours	14
Over 48 hours	9
Total	110

The relationship between the time of onset of jaundice and the outcome is shown in Table 7.

TABLE 7
RELATIONSHIP BETWEEN TIME OF ONSET OF JAUNDICE AND OUTCOME

Outcome	Time of Onset		
	At birth	Under 24 hours	Over 24 hours
Recovered ..	5	14	13
Died	27	41	10
Total ..	32	55	23

In a proportion of patients with icterus gravis neurological signs were present, possibly the result of the onset of nuclear jaundice (kernicterus).

HAEMOLYTIC ANAEMIA. Haemolytic anaemia is the least severe and the least fatal form of the disease. The patient may be anaemic at birth or may suddenly develop a waxen pallor in the first few days of extra-uterine life. There may be a mild and transient jaundice for the first few days of the disease. The anaemia tends to persist for several weeks. In three instances, where the condition had been overlooked in its earlier stages, a fatal outcome resulted.

Laboratory Investigations

The cord blood was tested by the Wassermann and Kahn techniques to exclude syphilis. The maternal blood was tested for its reaction with anti-Rh (anti-D) serum and for the presence of agglutinins. In this series only the technique for the demonstration of saline antibodies was available,

More recently the test for the presence of albumin (' blocking ') antibodies has come into general use. Wiener *et al.* (1948) have attempted to correlate the titre of albumin antibodies in the maternal serum with the severity of the disease process in the infant. Mollison and Cutbush (1949), however, do not believe that this correlation is reliable and many exceptions have been observed.

FIG. 1.—Hydrops foetalis affecting twins. Note large size of placenta. The twin on the left was slightly jaundiced, and the other twin severely macerated.

When the mother was Rh negative her serum was tested for the presence of antibodies at the third, seventh, and ninth months. A sudden rise in titre in the later months indicates a poor prognosis (Cummings, 1949).

In the later months of 1947 the direct Coombs test was carried out on the blood of all infants suspected of being affected by haemolytic disease. It was positive in all cases in which a diagnosis of haemolytic disease was finally made, and the strength of the reaction indicated the likely outcome. The reaction was strongest in the cases which terminated fatally. This is similar to the findings of Mollison and Cutbush (1949). It should be remembered, however, that the test is not infallible and a single negative result does not necessarily mean that the infant is not suffering from haemolytic disease. In cases of doubt the test should be repeated.

The blood was examined in all cases of haemolytic disease. In the case of live-born patients a full examination was carried out. Even in the case of the delivery of a macerated stillborn foetus a blood film, stained by the Leishman method, was examined, since the nucleated red cells retain their staining potential long after erythrocytes have become almost unrecognizable.

The findings vary from case to case. Different degrees of anaemia were present in affected patients and the degree of anaemia was not always related to the severity of the disease process. The haemoglobin values varied between 40% and 140% (Sahli). Some patients with icterus gravis and kernicterus had haemoglobin values of 120% and later died, whereas a few patients who were less severely affected and subsequently recovered had initial haemoglobin values of 70% or less. Nevertheless, as a general rule it was found that patients with a low haemoglobin level at birth were less likely to recover than those who had no initial severe anaemia. It is to be remembered that the haemoglobin level of an infant's blood is normally high at birth so that any value below 100% is indicative of anaemia.

The total red cell count also varied over a wide range from 1,000,000/c.mm. to 5,500,000/c.mm. The colour index was usually above unity. The reticulocyte count was high, and in two cases of haemolytic anaemia reached 50%.

When blood films were examined it was found that the red cells showed macrocytes, anisocytosis, and polychromasia. In two cases of haemolytic anaemia Howell-Jolly bodies were present.

Nucleated red cells were usually present in large numbers. There may be late or early normoblasts or erythroblasts. Occasionally haemocytoblasts were found.

Normally at birth nucleated red cells are less than 5% white cells. In haemolytic disease there were as many as 2,000% white cells. In general the most severely affected patients had large numbers of nucleated red cells in their circulating blood, but some exceptions were noted. These nucleated red cells usually disappear from the peripheral blood of normal infants by the third day of life. In haemolytic disease they are much more numerous and may persist for two weeks or more.

The patients affected by icterus gravis had low platelet counts (40-60,000/c.mm.) and the prothrombin index was frequently below 50% of the normal.

Biochemical investigations were carried out in the majority of cases of icterus gravis. It was found that the most useful tests were the icteric index and the estimation of serum (or plasma) bilirubin. The latter replaced the former as it is a more accurate procedure.

The icteric index was markedly increased in

icterus gravis and figures as high as 400 were achieved. When the icteric index rose above 200 the patient seldom survived. A very high icteric index was usually associated with a low haemoglobin level, but the correlation was not so close as in the series reported by Mollison and Cutbush (1949). The icteric index of cerebrospinal fluid ranged from 10 to 20.

The normal serum bilirubin level in newborn infants is 1-2 mg.%. In icterus gravis the range is 2-20 mg.% or even higher. Patients with a serum bilirubin level of over 7 mg.% seldom recover, whereas in those with a serum bilirubin level of 3 mg.% or less recovery is the rule. All patients with icterus gravis who subsequently developed kern-icterus had a high serum bilirubin level.

These laboratory investigations can be most helpful in the diagnosis of haemolytic disease, but it is important to remember that no single test is diagnostic. A final diagnosis can sometimes only be reached after a careful study of all available information concerning the patient. In general the most useful information is that derived from the result of the direct Coombs test on the infant's red cells, the presence of antibodies in the maternal serum, the haemoglobin value of the cord blood, the presence of numerous nucleated red cells in the peripheral blood of the infant, and a rise in the serum bilirubin level of the infant's blood.

Treatment of Haemolytic Disease

Since the discovery of the Rh blood groups a considerable controversy has arisen regarding the respective merits of Rh positive and Rh negative blood in transfusion therapy and the correct technique by which such blood should be administered to the affected infant. Most clinicians in this country and in America prefer to use Rh negative blood, and in the present series all patients treated by blood transfusion received Rh negative blood when the latter became available. Among the earlier cases 13 patients received blood which was almost certainly Rh positive (e.g. father's blood); seven recovered and six died.

Thirty-five patients were treated with Rh negative blood; 18 recovered and 17 died. The total amount of blood given to any one infant varied considerably. Some infants died after receiving only 90-100 ml. One infant received 1,100 ml. over a period of a month. The average amount transfused was 250 ml. and generally 15 ml. per lb. bodyweight was given at one time. The number of transfusions required varied according to the severity of the disease process and to the response of the infant to this form of therapy. A rapid fall in the haemoglobin level of the infant's blood was taken as a need for further transfusion. If the haemoglobin continued to fall in spite of transfusions the outcome was not likely to be favourable.

In this series the transfusions were simple and direct, and the route used in the earlier cases was via the anterior fontanelle (a method now abandoned) or the saphenous vein at the ankle. In the later cases the umbilical route was used whenever possible. More recently Wallerstein (1947), Diamond (1947), and Mollison (1948) have described a new transfusion technique by which a 90% substitution of the infant's blood may be effected. This technique had not been adopted during the period under review. Farquhar and Lewis (1949) have described the new technique, and it is now undergoing a period of trial but the results are less satisfactory than had been anticipated.

Mortality in Present Series

Of the 157 patients, 31 were stillborn (20%). Eighty-five (67%) of the remaining 126 live-born children died. The mortality figures analysed according to the type of haemolytic disease are shown in Table 8.

TABLE 8

MORTALITY OF LIVE-BORN PATIENTS

Type of Disease	Died	Recovered	Total	Mortality (%)
Hydrops foetalis	5	0	5	100
Icterus gravis ..	77	33	110	70
Haemolytic anaemia ..	3	8	11	27
Total ..	85	41	126	67

It must be emphasized that the majority of cases belonged to what may be termed the ' pre-Rh era,' and 78 of the 126 live-born cases were untreated. Of the 48 cases treated by blood transfusion, 23 died (48%). The newer methods of diagnosis and treatment were not in use during the period under review and time alone will tell whether they have reduced the mortality by any considerable degree.

Post-mortem Findings

Post-mortem examinations were carried out in 104 of the 116 cases of intra-uterine or extra-uterine death in this series.

Hydrops Foetalis. There were 36 cases of hydrops foetalis. Ten of these were macerated and five were live-born. Of these five only one lived for 24 hours. Eight were full-term foetuses and 28 were delivered prematurely. The average period of gestation of the latter was 33 weeks. Twelve were males and 19 were females. There was no record of the sex of the remaining five cases. Generalized subcutaneous oedema was one of the most constant features. It was less constant in the macerated foetus since there is a tendency for the foetus to dry *in utero* if birth is delayed. Hydrothorax, hydropericardium, and ascites were common. The fluid was generally clear and straw coloured in the stillborn and live-born, and blood-stained in the macerated

foetus. Petechial haemorrhages were found in the skin over the trunk, limbs, or face, and over the thymus, lungs, and heart. Occasionally subependymal petechiae led to intraventricular haemorrhage. Jaundice was not usually present, but in two cases there was a slight yellow tint of the skin and mucous membranes.

Icterus Gravis. There were 77 cases of icterus gravis and 35 of these showed kernicterus. Gilmour (1944) reported a predominance of four to three in favour of males. In this series there were 48 males and 29 females. Of these 59 were mature and 18 premature. Naturally the main feature was jaundice. The skin and mucous membranes were a bright golden-yellow colour and many of the infants had been covered by a golden-yellow vernix at birth. The jaundice varied in intensity from case to case and there was no direct correlation between the depth of the jaundice and the severity of the pathological lesions. All the cases with kernicterus were deeply jaundiced, but many equally jaundiced patients had not suffered from intracerebral lesions. Petechial haemorrhages into and under the pleura or pericardium were commonly found. Subcutaneous oedema was rare. The serous sacs sometimes contained bile-stained fluid, but the quantities were less than is usual in foetal hydrops.

Haemolytic Anaemia. There were three cases of haemolytic anaemia. Two were males, the third was a female, and all three were mature. One of the patients was slightly jaundiced, the others were not. There was slight subcutaneous oedema but no petechial haemorrhages were found. Nucleated red cells were numerous in the peripheral blood, and in one case numbered 200,000/c.mm. All types of red cell, from the pro-erythroblast to the mature erythrocyte, were found. Numerous reticulocytes were present and the erythrocytes showed anisocytosis and polychromasia.

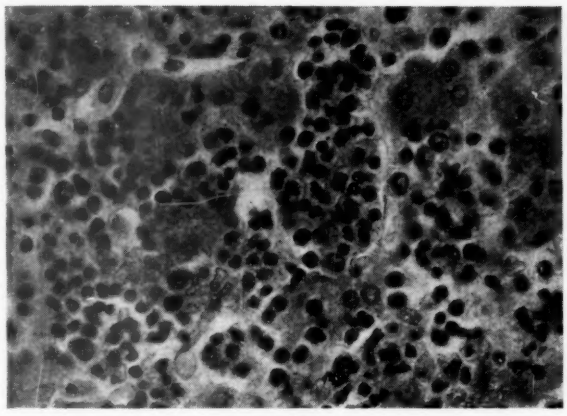
The Organs in Haemolytic Disease. The liver was usually enlarged and reddish-brown in colour in all types of haemolytic disease. In a few cases it was tough to cut, and in the severely macerated foetuses it was soft and diffluent. The Prussian blue reaction was usually positive. It was positive in all three cases of haemolytic anaemia. In icterus gravis the liver frequently showed some greenish discoloration as a result of bile-staining. No true examples of cirrhosis were found. On histological examination there was a marked amount of extramedullary haemopoiesis (Fig. 2). Foci of normoblasts and erythroblasts obscured the parenchyma in many cases. In hydrops foetalis the liver cells showed varying degrees of degeneration and had lost their structure in the macerated cases. In many cases there was a fine intercellular fibrosis and the cells in the central zones of the lobules showed early necrosis. In most instances the fibrosis was much less marked than may be found in congenital syphilis, but in two cases it was widespread and resembled cirrhosis of the liver in the macerated foetus described by Henderson (1942). In a few of the patients who had died from the effects of icterus gravis after the first week of life a fine diffuse fibrosis was found. In one case, the patient having died at the age of seven weeks, there was considerable periportal fibrosis with numerous new bile-ducts in the fibrous stroma. Plugs of bile in the intercellular canaliculi were not observed in hydrops foetalis and in haemolytic anaemia. In icterus gravis, however, the intercellular canaliculi were usually plugged with bile (Fig. 3). Haemosiderosis was present in nearly every case of hydrops foetalis (Fig. 4), in many cases of icterus gravis, and in all cases of haemolytic anaemia. The parenchymal cells and Kupffer cells in these cases contained the characteristic brown granules of haemosiderin, and the Prussian blue reaction was positive. The portal tracts showed numerous collections of haemopoietic cells. Normoblasts, erythroblasts, and eosinophil leucocytes were especially common, but myelocytes and lymphocytes were frequently observed.

The spleen was almost invariably enlarged and sometimes grossly so. The latter was especially true of the cases of haemolytic anaemia. The spleen was rather soft in hydrops foetalis, but firm in icterus gravis and haemolytic anaemia. The pulp was dark red in colour. The Prussian blue reaction was usually positive. In one case of icterus gravis the spleen had ruptured causing a massive fatal intraperitoneal haemorrhage. In one case of haemolytic anaemia there was a small superficial rupture of the spleen with extravasation of blood into the abdominal cavity. Microscopically, the capsule and trabeculae showed little change. The pulp was congested and numerous foci of haemopoiesis were present. The Malpighian bodies were usually absent in hydrops foetalis (Fig. 5), and poorly developed in the other types. Free haemosiderin was found in the subcapsular region or in histiocytes throughout the pulp.

The kidneys were often pale or macerated in hydrops foetalis, and bile-stained in icterus gravis. In one case of icterus gravis there was pyelonephritis. In a few cases histological examination showed that the lining epithelium of the convoluted tubules contained haemosiderin and the Prussian blue reaction was positive. Extramedullary haemopoiesis was less pronounced than in the liver or spleen. It was observed in the boundary zone of the cortex and in the perivascular connective tissue in the renal pelvis.

In approximately 60% of cases of hydrops foetalis the suprarenal glands showed a light yellow streaking of the inner cortex similar to that described by Gilmour (1944). Histologically, the cells in this region were vacuolated and distended with lipoid (Fig. 6). This change is not found in icterus gravis or haemolytic anaemia. A few foci of haemopoiesis may be found in the suprarenal cortex in all three types.

The lungs were collapsed in hydrops foetalis as a result of the hydrothorax. Subpleural petechiae



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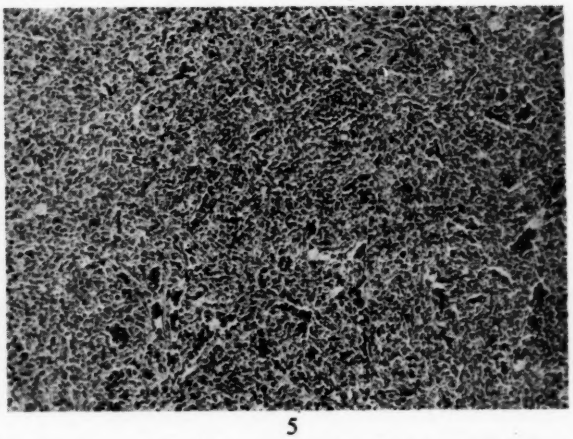

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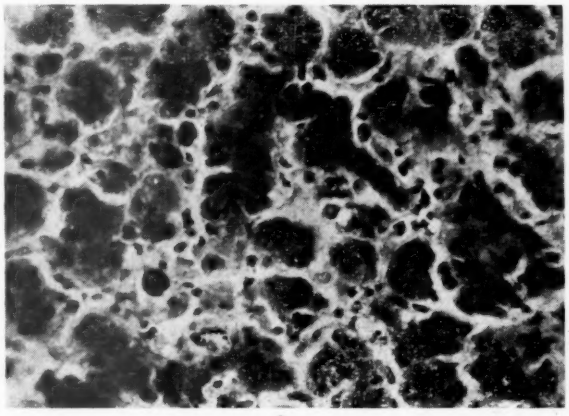

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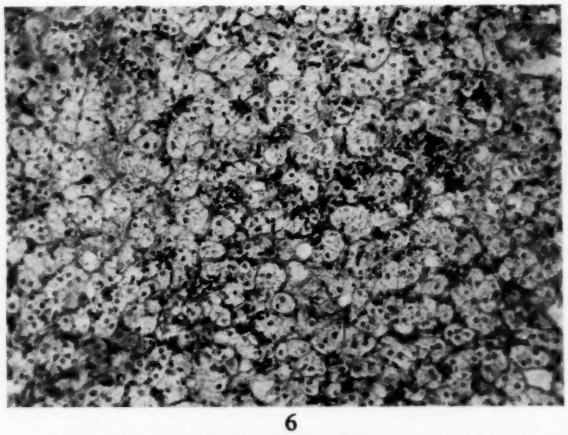

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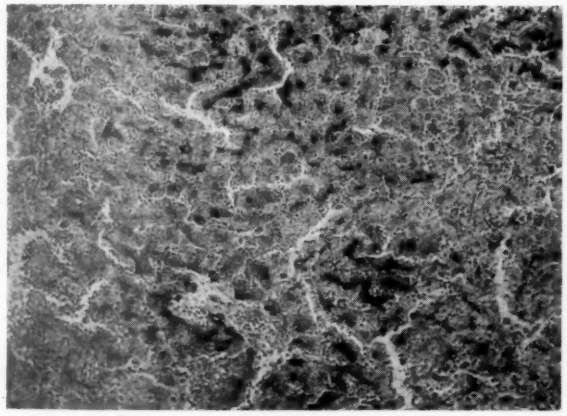

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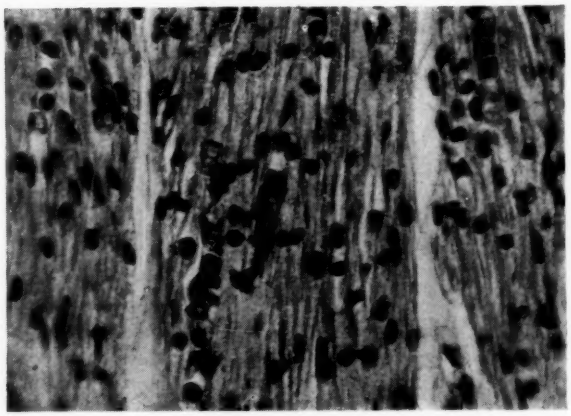

7

PLATE I

FIG. 2.—Liver 3×75. Haematoxylin and eosin. Extramedullary haemopoiesis.

FIG. 3.—Liver × 375. Haematoxylin and eosin. Plugs of bile in intercellular canaliculi. Case of icterus gravis.

FIG. 4.—Liver × 80. Prussian blue. Deposits of haemosiderin in parenchymal and Kupffer cells.

FIG. 5.—Spleen × 85. Haematoxylin and eosin. Marked haemopoiesis. Note absence of Malpighian bodies. Case of hydrops foetalis.

FIG. 6.—Suprarenal gland × 80. Haematoxylin and eosin. Vacuolation of cells of the cortex. Case of hydrops foetalis.

FIG. 7.—Heart × 400. Haematoxylin and eosin. Pronounced oedema of myocardial fibres. Case of hydrops foetalis.

were commonly found. In icterus gravis the lungs were occasionally the seat of massive haemorrhages. This occurrence was less frequent than might be expected. When present all the lobes may be firmly consolidated and dark red in colour. Large quantities of blood can be expressed from the cut surface. In a few instances it was complicated by a superadded bronchopneumonia. In haemolytic anaemia the lungs were pale and oedematous and areas of bronchopneumonic consolidation were present in two cases.

The heart was greatly enlarged in 12 cases of hydrops foetalis. This was not observed in icterus gravis or haemolytic anaemia. In the affected cases the myocardium was pale and the apparent hypertrophy was the result of oedema (Fig. 7).

The pancreas showed no change on macroscopic examination. Histological examination revealed the presence of a few foci of haemopoiesis in the perilobular connective tissue. In one case of hydrops foetalis the whole of the pancreatic stroma showed dense collections of nucleated red cells and eosinophil leucocytes. Large islets of Langerhans, as described by Gilmour (1944), were not a prominent feature in the hydrops foetalis cases in this series. They are more commonly found in infants whose mothers are diabetic or in the pre-diabetic phase.

Foci of haemopoiesis were frequently found in the thymus and thyroid glands.

Intracerebral lesions were uncommon in hydrops foetalis. In a few cases subependymal haemorrhages had ruptured into the lateral ventricles causing considerable damage. The basal ganglia showed no change. In icterus gravis diffuse bile-staining of the leptomeninges and cerebral cortex was frequently found. Kernicterus was present in 35 cases. Intracerebral damage was not present in haemolytic anaemia.

In two cases of hydrops foetalis the ossifying zone in the epiphyseal lines of the long bones was deeper than usual and rather yellow in colour. One case showed an abnormally broad layer of unossified cartilage in the epiphyseal region. The abnormalities of the bony trabeculae described by Gilmour (1944) were not observed.

The bone marrow was highly reactive and nucleated red cells were extremely abundant in all types of haemolytic disease. All stages of development from the haemocytoblast to the erythrocyte were seen. There was an increase in the number of eosinophil leucocytes.

The placenta in hydrops foetalis was enlarged, pale, and oedematous. The weight of this organ was greatly increased and frequently approximated to half the body weight of the affected infant. The villi were large, swollen, and oedematous. Foci of haemopoiesis were rarely found but the foetal capillaries contained large numbers of nucleated red cells. The stroma cells were enlarged, vacuolated, but not increased in number. Occasionally the syncytial cells were prominent.

Discussion

There have been great advances in knowledge concerning the development of haemolytic disease within the last 20 years. Before this the individual types of haemolytic disease were not recognized as belonging to a single disease complex. Diamond, Blackfan, and Baty (1932) assembled the three types, hydrops foetalis, icterus gravis, and haemolytic anaemia, under the heading 'erythroblastosis foetalis.' The work of Parsons *et al.* (1933) concerning what they termed the 'erythronoclastic anaemias,' served to demonstrate the importance of red cell destruction as a factor in the development of haemolytic disease. With the discovery of the Rh factor by Landsteiner and Wiener (1940) and of the aetiological importance of the Rh blood groups by Levine *et al.* (1941), the development of haemolytic disease in the foetus was more clearly understood.

The iso-immunization of the mother by a Rh positive child or by transfusion with Rh positive blood has now been clearly established. New serological methods of diagnosis have been introduced and transfusion of the infant with Rh negative blood has become the recognized method of treating affected subjects. In spite of these advances, however, there is still quite a high mortality. The figures obtained in this series are not truly representative. Nevertheless, the mortality is considerable and many cases come to post-mortem examination. It is for this reason that the pathological features of haemolytic disease have been described in some detail. Mistakes in serological diagnosis occasionally occur and the pathologist may be asked to confirm or refute a diagnosis of haemolytic disease.

Hydrops foetalis resulting from haemolytic disease must be distinguished from congenital syphilis, congenital heart disease, and idiopathic hydrops. Occasionally the offspring of a diabetic mother may be hydropic.

Congenital syphilis was confused with haemolytic disease for many years. Hepato-splenomegaly and erythroblastaemia are found in both diseases. The Wassermann and Kahn tests to exclude syphilis, and the Coombs test to detect sensitization, have helped to distinguish the two diseases. A full post-mortem examination should be carried out in all doubtful cases. For example, I performed a post-mortem examination on an infant suspected of having haemolytic disease. Wassermann and Kahn tests had not been carried out, and the mother was Rh negative. The liver and spleen were enlarged and the former showed a marked degree of haemopoiesis of a primitive type. No spirochaetes were found in either organ. The pancreas,

however, showed well marked fibrosis of a syphilitic type.

It is in the idiopathic form of hydrops foetalis that a full necropsy is most essential. Potter (1946) correctly pointed out that the diagnosis of hydrops resulting from haemolytic disease must be made only after very careful histological examination of the tissues. The condition of the placenta is also a valuable aid in correct diagnosis. Hydrops foetalis of the idiopathic type is of obscure origin. It occurs not infrequently in first pregnancies and may be associated with congenital malformations such as spina bifida or diaphragmatic hernia. These hydropic foetuses are nearly always followed by normal children. They show no evidence of erythroblastosis on post-mortem examination. Such a careful examination saves the parents much needless anxiety.

Wiener and Sonn (1946) have described an instance where a stillbirth was thought to have been caused by haemolytic disease but further examination revealed diabetes mellitus in the mother. Examination of the pancreas in the offspring of diabetic and pre-diabetic mothers will reveal the presence of giant islets of Langerhans.

Icterus gravis neonatorum must be distinguished from physiological jaundice of the newborn, congenital atresia of the bile ducts, congenital syphilis, and neonatal sepsis. The problem of differentiating between the various types of jaundice in the newborn is now a familiar one.

Neonatal sepsis was regarded as a cause of haemolytic disease before the Rh blood groups were recognized. In a case of neonatal infection jaundice may appear after a few days and anaemia may develop. Nucleated red cells are to be found in the peripheral blood. Neonatal sepsis may complicate an existing haemolytic disease in which case the serological investigations will be positive. This is the probable explanation of the cases described by de Bruyne and van Creveld (1948).

Haemolytic anaemia must be distinguished from haemorrhagic disease of the newborn and other blood diseases of the neonatal period. Haemorrhagic disease of the newborn is a result of hypoprothrombinaemia and reacts well to vitamin K therapy. There is neither enlargement of liver and spleen nor jaundice. The degree of anaemia is seldom severe. Primary blood diseases, such as aplastic anaemia and leukaemia, are rare in the neonatal period. Many cases at this stage of life formerly diagnosed as leukaemia were probably haemolytic disease.

Modern serological tests have enabled a correct diagnosis to be made to-day more often. This is especially true of the milder examples of haemolytic disease which may have been overlooked before. More rapid methods of diagnosis naturally lead to the institution of specific therapy under more favourable conditions. The mainstay of therapy in haemolytic disease is now Rh negative blood transfusion. This should be given as early as possible in severe cases. The amount of blood used should be adequate, but transfusions should not be repeated more frequently than is absolutely necessary. The technique is a matter of individual preference. The exchange-replacement transfusion technique is the more formidable procedure and is mainly suitable for use in well-equipped institutions. Unfortunately, transfusion therapy has little effect in hydrops foetalis. Whether the new techniques will redress the balance is a matter for further investigation. In icterus gravis the most favourable results follow the early institution of transfusion therapy. Haemolytic anaemia is the mildest form of the disease and may require no specific treatment, but these patients should be carefully watched lest a sudden fall in haemoglobin occur when prompt and adequate blood transfusion should suffice.

With regard to prognosis in haemolytic disease, it is important to consider the progress of both mother and infant. The mother is suffering from a state of sensitization to a blood antigen she herself does not possess, and the clinician must give careful advice about future pregnancies. The infant is affected by a disease process which may vary considerably in intensity. Potter (1948) and many others have stated that haemolytic disease is rare in the first pregnancy and when it occurs is likely to prove mild in character, provided the mother has not previously received Rh incompatible blood. In the present series this was not so clearly demonstrated. Ten of the 149 women were pregnant for the first time. Three of the offspring were stillborn exhibiting hydrops foetalis, five died from icterus gravis, and only two recovered. It is reasonable to suppose that women who bear offspring suffering from haemolytic disease in their first pregnancy are unduly susceptible to sensitization by a foreign blood antigen and thus the effect on the foetus is likely to be severe.

Potter (1948) has also remarked that the offspring of early pregnancies exhibit a milder form of the disease than those born in later pregnancies. It was found in the present series that the maximum incidence of haemolytic disease occurred in the offspring of the second and third pregnancies and so the maximum number of recoveries will also be found in this period. Stillbirths with hydrops foetalis are, however, proportionally more common

in later pregnancies. Whether the mother who has borne one child exhibiting haemolytic disease is likely to have a normal infant in a subsequent pregnancy is a complex question. If the father is homozygous Rh positive all the offspring will be Rh positive and liable to suffer from haemolytic disease. If, on the other hand, he is heterozygous Rh positive there is an even chance of future children escaping haemolytic disease. It must be remembered that genotyping is by no means absolutely accurate owing to the lack of rarer sera, and also errors in typing the father's blood are not uncommon.

A study of the cases in this series shows that certain probabilities are of some help in judging the prognosis. For instance, it is highly probable that a mother who has been delivered of a number of consecutive stillborn hydropic foetuses will continue to produce such offspring in subsequent pregnancies. Such a mother should be advised against further pregnancies, and if one occurs a therapeutic abortion should be considered. In contrast to these patients, it is very probable that women who have had one child mildly affected with haemolytic disease will produce future infants who are only mildly affected. One patient in this series had one infant suffering from severe icterus who subsequently died; a second infant also had icterus gravis with kernicterus and subsequently died; the third was only very mildly affected and recovered. Thus, considerable care must be taken in venturing a prognosis.

One final danger to the mother must be mentioned. It is absolutely essential to ensure that any blood given in the treatment of severe post-partum or other haemorrhage is of the correct Rh type. If an Rh negative woman, who is sensitized to Rh antigen, is transfused with blood which is not Rh negative the result may well be disastrous.

The future outlook in affected offspring depends on the variety of haemolytic disease encountered. In hydrops foetalis the outlook is grave, whereas in haemolytic anaemia it is good. In icterus gravis the prognosis depends on the severity and on the success of transfusion therapy. In general, a very severe degree of jaundice at birth, a low haemoglobin level in the cord blood, and a high serum bilirubin level are signs of a poor chance of recovery. Patients with evidence of neurological involvement seldom survive.

Each patient, both mother and child, requires careful study and no set of rules can be devised to meet all contingencies.

Summary

This study has dealt with the features presented by 157 cases of haemolytic disease in the newborn, including 36 examples of hydrops foetalis, 110 of icterus gravis, and 11 of haemolytic anaemia. The pathological changes found in all forms of the disease have been noted. The obstetrical histories of the mothers of the affected infants have been investigated and the various factors of prognostic significance examined. The clinical features of the affected patients and the criteria of severity were similar to those reported by other workers. An unusual feature was the severity of the disease process in ten women who were pregnant for the first time.

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PART II : NUCLEAR JAUNDICE (KERNICTERUS)

The first description of this unfortunate sequel to haemolytic disease was that by Orth (1875) who used the term nuclear jaundice. Schmorl (1903) introduced the word *Kernikterus* in his description which was the first detailed report of the pathological features of the cerebral lesions.

It soon became obvious that kernicterus was found in close association with icterus gravis neonatorum. The familial aspect of the condition was dealt with in the earlier literature (Beneke, 1907; Pfannenstiel, 1908; Esch, 1908; Pfältzer, 1914; Ylppo, 1918; Thorling, 1922; Heilgenberg, 1925). Spiller (1915) reported three cases of mental deficiency in which severe jaundice had occurred during the neonatal period. Occasional instances of kernicterus were reported by various authors (Hart, 1917; Palm, 1919; Paul, 1924; de Lange, 1925; Hoffmann and Hausmann, 1926; Greenwald and Messer, 1927; Diamond and van Creveld, 1937; Westrienen and de Lange, 1937). Detailed reports of the histological findings in kernicterus were given by Zimmerman and Yannet (1933; 1935) and by Fitzgerald, Greenfield, and Kounine (1939). Up to this date the association of kernicterus with icterus gravis had been generally recognized. With the discovery of the Rh blood groups a new approach to the problem was instituted. Recent reviews of the subject are those of Docter (1945), Vaughan (1946), Stiller (1947), and Lande (1948).

In spite of the great interest which has been taken in these cases many problems concerning the development of kernicterus have remained unsolved. One of these problems is the time of onset of nuclear jaundice, and this will be specially considered.

Clinical Features of Kernicterus

Of the 110 patients affected by icterus gravis in this series, 37 showed kernicterus (33·6%). The condition may be considered in two stages, the acute stage, which is the stage most frequently seen and occurs at the height of jaundice in the early neonatal period, and the chronic stage which follows the acute stage in the few patients who survive beyond the first week of extra-uterine life.

Acute Stage. This is the stage of acute irritation of the cerebral ganglia. The infants show evidence of severe cerebral irritation, with clonic and tonic movements going on to convulsions, hypertonia, and opisthotonos. In between these spasms of hyperactivity the patients are drowsy and apathetic. They cry a good deal and have difficulty in taking their feeds. The infants become steadily weaker and the majority die before the fifth day of extra-uterine life.

In this series 28 of the patients (76%) died before the second week of life. They become jaundiced shortly after birth (or were jaundiced at birth) and the jaundice steadily deepened. The liver and spleen were palpable. Evidence of cerebral irritation soon became manifest and twitching of the limbs, convulsions, and opisthotonos were noted.

Examination of the peripheral blood revealed the presence of large numbers of nucleated red cells and the serum bilirubin level was 10-20 mg.%. The degree of anaemia was variable. One patient had a haemoglobin level of 70% (Sahli) whereas another had a haemoglobin level of 120%. All ranges between these extremes were noted. In spite of treatment the infants collapsed and died. A further four infants died in the second week of life, two at nine days, and two at twelve days. One other infant died on the fourteenth day. All showed clear signs of neurological involvement. Thus only four infants survived beyond the acute or early chronic stage.

Chronic Stage. After the first week of extra-uterine life, should the infant survive so long, irreversible change occurs in the basal ganglia and the other cerebral nuclei. Clinical evidence of derangement of the extrapyramidal system is now more obvious. Before this, in the acute stage, the signs were those of cerebral irritation and were not in themselves pathognomonic of kernicterus, although in association with icterus gravis, they take on an added significance. Lande (1948) divided her patients into four clinically distinct groups:

> Group 1: Patients exhibiting choreo-athetosis as a result of involvement of the corpus striatum and globus pallidus.
>
> Group 2: Patients showing persistent spasticity from the involvement of the pyramidal and extra-pyramidal systems.
>
> Group 3: Patients showing ataxia and disturbance of balance.
>
> Group 4: Patients in whom atonic diplegia is the predominant sign.

As that author points out, many patients show a combination of physical signs from all groups. In addition, cranial nerve lesions may be present and blindness, strabismus, and deafness are not uncommon. These have also been noted by Zimmerman and Yannet (1935). Recently kernicterus has been cited as a cause of infantile cerebral palsy (Evans, 1948).

Mental retardation may be a prominent feature among patients in this stage, and it is difficult to assess how much this retardation is due to cerebral damage and how much to the physical incapacity which the disease promotes. The patients with severe choreo-athetosis, for example, have difficulty in remaining still for an instant.

The further development of patients in the chronic stage is very slow. They may not be able to sit

up or even hold their head up at one year of age. Walking may be delayed up to the sixth year or longer (Lande, 1948). Feeding themselves is a difficulty and training in toilet habits is prolonged.

In the present series only four patients survived to this stage. One patient improved considerably but had marked choreo-athetosis. Another child is also still alive at the time of writing. He has learned to walk at four years, though with some difficulty, and there is no evidence of mental impairment. The chief neurological feature is hypotonia rather than spasticity. The remaining two patients died at the age of 4 months and 17 months respectively. The former developed jaundice 24 hours after birth and exhibited head retraction and opisthotonos on the fourth day. The jaundice disappeared after six weeks but evidence of cerebral involvement persisted. She had severe spasms of the limbs, and the arms and legs were spastic. The reflexes were absent and Kernig's sign was present. She died at the age of four months as a result of acute bronchitis. The last child died at the age of 17 months and no satisfactory cause of death was found at post-mortem examination. In no instance did any general sign or symptom differentiate these patients from others with icterus gravis before the onset of kernicterus.

Time of Onset of Jaundice

As will be seen from Table 1, jaundice was present in the great majority of patients by the end of the first day and was present at birth in 14 out of 37 patients.

TABLE 1
TIME OF ONSET OF JAUNDICE

	No. of Patients
Present at birth	14
Present within 6 hours after birth	2
Present within 6-12 hours after birth	5
Present within 12-24 hours after birth	13
Present within 24-48 hours after birth	3
Total	37

Rhesus Blood Groups

Serological investigations were carried out on 15 of the 37 patients. In 13 of these 15 patients the usual pattern of Rh negative mother and Rh positive father and child was obtained. Five of the 13 Rh negative mothers had antibodies in their serum.

Age at Death in Fatal Cases

The age of the infant when death supervened is shown in Table 2. It will be noted that the great majority succumb by the end of the first week of extra-uterine life. Of these, the greater number die within the first 72 hours.

TABLE 2
ANALYSIS OF AGE AT DEATH IN FATAL CASES

Time at Death	No. of Patients
18 hours after birth	1
36 hours after birth	4
2 days after birth	6
3 days after birth	8
4 days after birth	1
5 days after birth	3
6 days after birth	1
7 days after birth	4
9 days after birth	2
12 days after birth	2
14 days after birth	1
4 months after birth	1
17 months after birth	1
Total	35

Cause of Death in Fatal Cases

Most of the patients died from the systemic upset associated with icterus gravis and aggravated by kernicterus. Complications such as intrapulmonary haemorrhage, pneumonia, and meningitis may also occur, and a summary of the cause of death in the 35 cases is shown in Table 3.

TABLE 3
SUMMARY OF CAUSES OF DEATH

Cause of Death	No. of Cases
General effects of icterus gravis	23
Pneumonia	2
Intrapulmonary haemorrhage	2
Subarachnoid haemorrhage	2
Intraventricular haemorrhage	3
Acute leptomeningitis	1
Acute bronchitis	1
Late effects of kernicterus	1
Total	35

Vaughan (1946) stresses the importance of severe respiratory distress resulting from intrapulmonary haemorrhage as a factor in the sudden collapse. As may be seen from Table 3 only two patients suffered from this complication. Hawksley and Lightwood (1934) and Mollison and Cutbush (1949) are inclined to the view that medullary failure plays a part in the early fatal outcome.

Treatment of Patients with Kernicterus

Vaughan (1946) remarks that the only benefit from blood transfusion to patients with kernicterus is that resulting from the replacement of cells in those who are severely anaemic, and, as severe anaemia was not invariably present, such therapy had disappointing results.

In the present series the mortality was high. Thirty-three of the 37 patients died within a fortnight of birth (90%). Only two survive at the time of writing. One received a total of 265 ml. of Rh negative blood and the other was given blood of unknown Rh group. One other patient received a transfusion of blood whose Rh group was unspecified, but died. Five patients received transfusions of Rh negative blood and all died. The remaining 29 patients received no blood transfusions and all died. It is obvious that too small a number were treated by blood transfusion to permit of comment.

Vaughan (1946) found that no case of kernicterus occurred when infants with icterus gravis were transfused on the first day of life with Rh positive blood. The majority of workers, however, do not recommend the use of Rh positive blood in the treatment of haemolytic disease.

Blood transfusion therapy has obviously no place in the treatment of the chronic case as irremediable damage to the cerebral cortex has already occurred. Careful training of these patients to use their mind and body as much as their physical disabilities will permit has done much to mitigate the degree of functional incapacity. Docter (1945) states that patients showing severe spasticity in the early weeks tend to improve as they grow older if adequate care is exercised.

Pathological Features of Kernicterus

Morbid Anatomy. The morbid anatomy of what may be termed the chronic stage of kernicterus has been described in the papers of Zimmerman and Yannet (1935) and of Fitzgerald *et al.* (1939). The anatomical features of the acute stage are well known but have received less study.

In this series the anatomical findings in the 35 fatal cases will be described. Of these 35 patients, 23 were males and 12 females. (Litchfield, 1945, suggested that the lesion was less common in the female.) Twenty-five were full-term infants and only ten were premature. Kernicterus was found in two sets of twins, each twin being affected, and in two other pairs, one twin only was affected. These twins account for five of the eleven premature infants.

In the acute stage the infants are very jaundiced and a few subcutaneous petechiae may be present. One infant was also very oedematous.

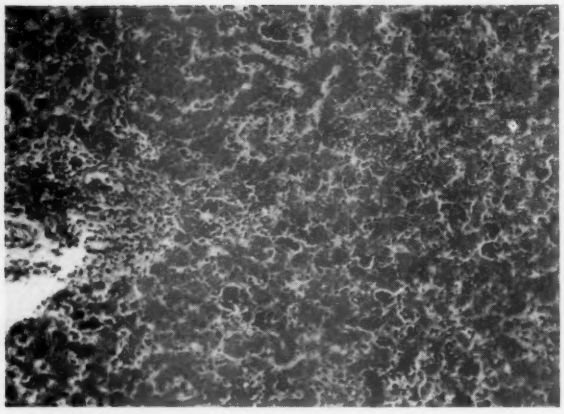
The liver was usually moderately enlarged and brownish red in colour. The Prussian blue reaction was positive. The spleen was greatly enlarged in 26 cases and moderately enlarged in a further six cases. In three cases it was of normal size. The splenic pulp was dark red in colour, and the Prussian blue reaction was frequently positive. The kidneys were of normal size and were frequently bile-stained. The lungs showed intrapulmonary haemorrhage in two cases and in another two cases bronchopneumonia had developed. The leptomeninges were intensely bile-stained. The brain was usually found to be diffusely bile-stained and pale yellow in colour. On section certain nuclei were intensely bile-stained and were bright orange-yellow in colour. The nuclei liable to be affected were the corpus striatum, thalamus, corpus Luysii, globus pallidus, cornu ammonis, putamen, corpora mamillaria, subthalamic nuclei, hippocampus, third nerve nuclei, the nuclei in the floor of the fourth ventricle, the inferior olives, the grey matter of the medulla, the dentate nuclei, and the flocculus of the cerebellum. The anterior and posterior horns of the spinal cord were also frequently involved. These nuclear areas were not necessarily all affected in any one case. The cornu ammonis, the basal ganglia, inferior olives, and dentate nuclei were usually stained. In the great majority of cases the inferior olivary nucleus was bright orange-yellow in colour and had a more striking appearance than that shown by the basal ganglia. On rare occasions the white matter around the posterior horns of the lateral ventricles was also deeply stained by bile. This latter feature was observed in one case. The other organs of the body showed no pathological change.

Two patients in this series survived beyond the neonatal period. One died at the age of four months as a result of acute bronchitis. At post-mortem examination there was evidence of acute bronchitis and pulmonary congestion. There was no bile-staining of any part. The second patient died at the age of 17 months. No satisfactory cause of death was found at necropsy and none of the organs showed any pathological change. In neither patient did the brain show any abnormality on external examination. On section the only change found was in the cornu ammonis. This was rather smaller than usual.

Morbid Histology. There were many foci of extramedullary haemopoiesis in the liver in just over half the cases and fairly numerous foci were found in the remainder (Fig. 1). Many of the intercellular canaliculi were plugged with bile and the liver cells contained bile pigment. More occasionally the parenchymal cells contained haemosiderin and the Prussian blue reaction was positive. In the older infants there was slight fatty degeneration or early necrosis of cells in the central zones of the lobules and a slight increase in the periportal fibrous tissue. There was no cirrhosis in any case. Haemopoiesis was not a marked feature in patients who had died after the first week (Fig. 2). In the patients who had died in the chronic stage the liver was perfectly normal.

Numerous foci of extramedullary haemopoiesis were present in the spleen in the acute cases. Numerous histiocytes in the pulp, especially in the subcapsular region, contained haemosiderin, and the Prussian blue reaction was positive (Fig. 3). No fibrosis had occurred.

The cells lining the convoluted tubules contained bile-pigment in a few cases. In some others there were foci of haemopoiesis in the boundary zone of the cortex and in the peripelvic connective tissue.



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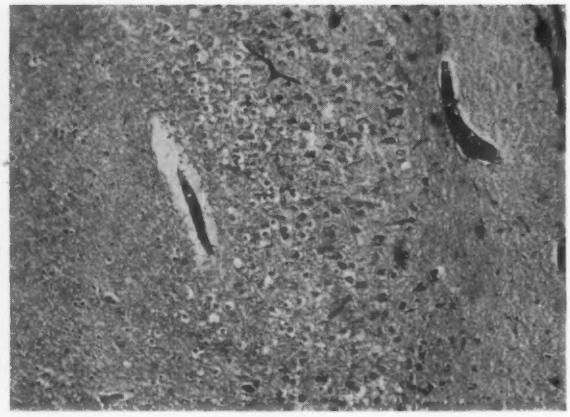

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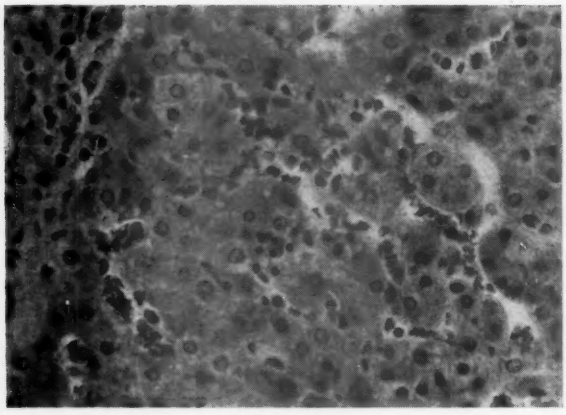

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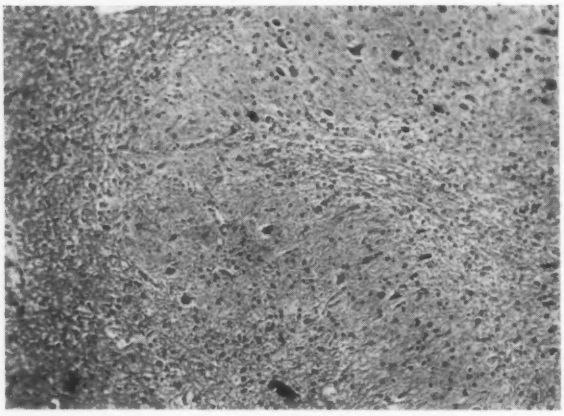

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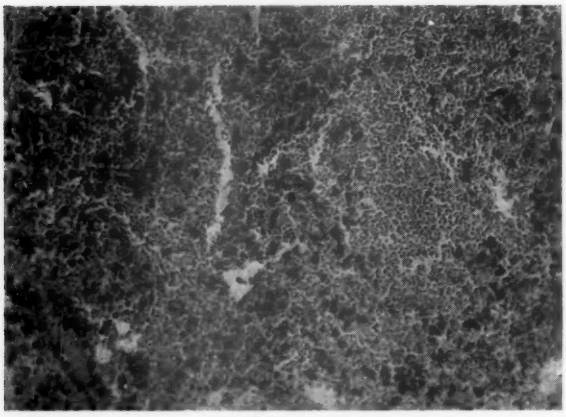

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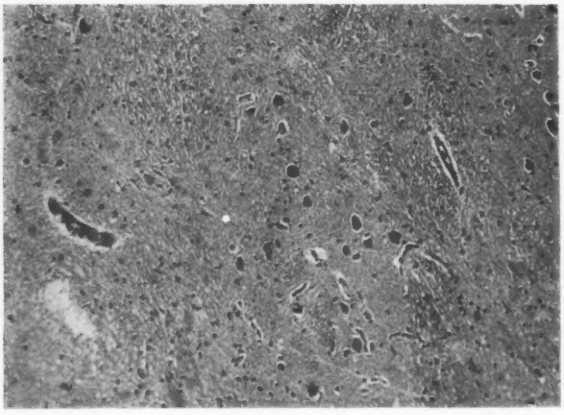

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PLATE II

FIG. 1.—Liver × 80. Haematoxylin and eosin. Numerous foci of haemopoiesis. Case of icterus gravis showing kernicterus (acute stage).

FIG. 2.—Liver × 240. Haematoxylin and eosin. Only a few foci of normoblasts present. Case of icterus gravis showing kernicterus (early chronic stage).

FIG. 3.—Spleen × 90. Prussian blue. Extensive haemosiderosis. Kernicterus (acute stage).

FIG. 4.—Brain (basal ganglia) × 80. Haematoxylin and eosin. Ganglion cells are vacuolated. Case of kernicterus (early chronic stage).

FIG. 5.—Brain (cerebellum) × 80. Mallory. Neuronal loss in dentate nucleus and astrocytic replacement. Kernicterus (chronic stage).

FIG. 6.—Brain (basal ganglia) × 80. Mallory. Neuronal loss and astrocytic replacement. Kernicterus (chronic stage).

Intrapulmonary haemorrhage was severe in two cases and very slight in a third. The interstitial tissue and alveoli were flooded with fresh blood. Pneumonia was present in two cases.

The definition of the acute stage includes those patients who died before the end of the first week of extra-uterine life. Histological examination of the brain in these cases failed to reveal any features which differed from those of normal brains in infants of the same age. Most of the sections examined showed no structural change whatsoever. A few showed chromatolysis of the neurones and a few ganglia showed cell loss, but these changes are common necropsy findings in children of this age. Two cases showed yellow staining of the cells in the cornu ammonis, but the cells were not otherwise altered. In one case an acute leptomeningitis and ventriculitis masked the histological appearance.

The early chronic stage corresponds to the clinical stage when signs of extrapyramidal involvement are more striking features than generalized cerebral irritation. It occurs about the end of the first week of life. The areas which were seen to be pigmented on macroscopical examination now showed some loosening up of the cerebral tissue and the formation of globules of lipoid (Fig. 4). Slight astrocytic reaction may be present. It is interesting to note that Zimmerman and Yannet (1933) examined the brain of a child with kernicterus who had died aged 11 days. Even at this age, they stated that ' it was impossible to determine whether the icteric ganglion cells were injured.' They did, however, find numerous fat granule cells in the centrum ovale. Thus the earliest irreversible change in the affected areas would seem to be a necrosis of cerebral tissue with slight astrocytic replacement.

There are two patients in this series who died in the chronic stage. In the first, who died at the age of four months, there was severe cell loss and astrocytic replacement in the dentate gyrus. There was loss of large cells and astrocyte replacement in the globus pallidus. Focal neuronal loss had occurred in the dentate nuclei (Fig. 5). In the putamen, inferior olives, and third nerve nucleus there were small foci of polymorphonuclear leucocytes, lymphocytes, and microglial cells.

In the second patient (died at the age of 17 months) the spinal cord, medulla, frontal, parietal and occipital cortex showed no abnormality. In the basal ganglia there were focal areas of nerve cell loss with a marked reparative gliosis (Fig. 6). In the cornu ammonis there was complete disappearance of the nerve cells of the fascia dentata and of the terminal nerve cells of the subiculum. There was an increase of astrocytes in this region.

It is interesting to compare these findings with those of Zimmerman and Yannet (1935). The changes in their case were even more widespread. The optic nerves, reticulo-spinal, rubrospinal, and spino-cerebellar tracts showed demyelination. On the other hand, they found no astrocytic replacement in any region and describe the destructive process as one of necrobiosis.

Vaughan (1946) failed to find necrobiosis in his fatal cases of kernicterus, and states that ' in certain of the brains where kernicterus was found in gross sections, no microscopic abnormality whatsoever was encountered.' This is not surprising because nearly all his fatal cases were patients dying in the acute stage when no irreversible histological change occurs.

Discussion

There were 37 patients showing evidence of kernicterus in a total of 110 patients suffering from icterus gravis, an incidence of 33%. Of these 110 jaundiced patients, 47 died within the first week of life and, of these 47 patients, 31 were found to have kernicterus at post-mortem examination.

Thirty-three patients who had suffered from icterus gravis survived beyond the neonatal period. Four of these (12%) exhibited neurological signs of kernicterus. Cappell (1947a) stated that kernicterus might be expected in 40% of cases of icterus gravis in the neonatal period and among 12% of the survivors. His figures and those of this series are very similar.

The total number of cases of haemolytic disease of all types in the present series was 157, and kernicterus was present in 37 instances (23%).

Kernicterus does not occur in hydrops foetalis, even when these foetuses are jaundiced. It is not seen in patients with icterus gravis who die within an hour or two of birth. The earliest death in a child showing kernicterus occurred 18 hours after birth and the jaundice was first noted six hours after birth. The kernicterus therefore probably developed within the first 12 hours after birth. Parsons (1947) also reported a patient with kernicterus who died 18 hours after birth. The nuclear staining, while causing intense cerebral irritation, does not appear to cause immediate irreversible damage to the affected cells. On the contrary, at necropsy, the affected cells may be bile-stained but not structurally altered. This lack of histological change may persist as late as the sixth to eighth day of extra-uterine life or slightly later. At the end of this period irreversible cellular damage occurs with neuronal destruction and gradual astrocytic replacement. The cornu ammonis is the first to be so affected, and the optic nerves and grey matter of the spinal cord are among the last to undergo such structural alteration. Thus in the acute stage of the disease the presence of bilirubin in the cells causes intense cerebral irritation which leads to tonic and clonic movements and opisthotonos. These severe spasms are broken by periods of lethargy and drowsiness. In the early chronic stage the corpus

striatum shows the most severe cytological change and this leads to the development of choreoathetosis which is such a well-marked feature of the condition. In the later chronic stage the changes are widespread and affect structures outside the basal ganglia or even the extrapyramidal system. Lande (1948) has described patients with deafness, blindness, strabismus, and cranial nerve palsies. Such symptoms are not surprising in view of the histological findings in the case of Zimmerman and Yannet (1935) and of the changes present in the patient in this series who died at the age of four months. In the former there was demyelination of the optic nerves, optic chiasma, and spinal tracts as well as damage to the basal ganglia and extrapyramidal system; in the latter the third cranial nerve nucleus and the dentate nuclei of the cerebellum were severely involved. Thus in the later cases of kernicterus, neurological signs referable to damage in the cranial nerve nuclei, optic nerves, and spinal cord are to be anticipated, in addition to evidence of lesions in the basal ganglia and extrapyramidal system. The condition affects not only the latter structures but is widely present throughout the nuclear aggregations of cerebrum, brain stem, cerebellum, and grey matter of the spinal cord.

Even at the beginning of this century it became recognized that kernicterus was almost always associated with icterus gravis neonatorum wherever erythroblastosis was a prominent feature. The other major cause of severe jaundice of the newborn, congenital obliteration of the bile ducts, had failed to yield a single instance of kernicterus. It is interesting to note that Pasachoff (1935) has described a case of kernicterus in which the patient also had atresia of the bile ducts. The author makes it quite clear, however, that the patient was also affected by haemolytic disease and he stresses the latter, rather than the former, as the primary aetiological factor in the development of the nuclear jaundice.

At one time neonatal sepsis was believed to be an aetiological factor in the development of icterus gravis and of kernicterus. Beneke (1907) believed that organisms entered the blood stream via erosions (stigmata) in the gastric mucous membrane. Knoepfelmacher (1910), Pfältzer (1914), and Thorling (1922) all obtained positive cultures from post-mortem material in kernicterus cases and were strongly in favour of an infective basis for the disease. Pfältzer (1914) even went so far as to name *Bact. coli* as the causative organism. Dunham (1933) found jaundice in 14 instances out of 40 cases of neonatal sepsis. Zimmerman and Yannet (1933) obtained *Bact. coli* from the blood in Case 2 and Case 3 of this series. They were inclined to favour the sepsis hypothesis for the development of nuclear jaundice. Biemond and van Creveld (1937) reported two cases of kernicterus and icterus gravis where severe umbilical sepsis was also present. Since the discovery of the Rh blood groups the influence of sepsis in the aetiology of icterus gravis and kernicterus has received less attention. Recently, however, a further series of four cases of kernicterus complicating icterus gravis has been reported by de Bruyne and van Creveld (1948). In all these cases severe umbilical sepsis was present. Cases 1 and 2 of their new series were siblings of the earlier patients of van Creveld (1937) and evidence of iso-immunization to Rh antigens was now present in both mothers. The mother of Case 3 also had anti-Rh agglutinations in her serum. The mother of Case 4 was Rh positive but her serum had an anti-A agglutination titre of 1/512. These serological findings throw some doubt on the validity of the infective hypothesis. Sepsis played no part in the development of kernicterus in the patients in my series.

Orth (1875) believed that there was a primary necrosis of parts of the brain and that these areas were subsequently pigmented. Schmorl (1903) suggested that the primary change was a cell necrosis either resulting from vascular damage or from a toxic degeneration of the cell. He believed that the toxin responsible might be bile itself. Hart (1917) also thought that the ganglion cells were injured by bile or became pigmented with the latter following injury by some unknown toxin. As Zimmerman and Yannet (1933) correctly pointed out, 'any consideration of the pathogenesis of kernicterus must take into account the factors underlying the development of icterus as well as those responsible for changes in the nervous system.' The link between the liver upset and the brain injury had already attracted the attention of workers in this field. Hoffmann and Hausmann (1926) suggested that the liver damage took the form of a hepatitis which resulted in the liberation of lipolytic substances which were responsible for cerebral necrosis. Several experimental workers investigated the possibility of liver disease leading to cerebral damage. Fuchs (1917) fed experimental animals on guanidine which caused liver damage and subsequent changes in the brain. Pollak (1921) examined the brains of the animals who had undergone such an experiment and found an inflammatory reaction in the basal ganglia with neuronal loss. The damage was diffuse, however, and not wholly confined to the nuclear masses. Mella (1924) injected manganese intraperitoneally into *Macacus*

rhesus monkeys and produced nuclear loss in the putamen and caudate nuclei. In two of his animals hepatic fibrosis occurred. Crandall and Weil (1933) ligated the common bile duct in rats and caused degeneration of the corpus striatum. While these experiments failed to reproduce kernicterus they did seem to indicate a link between hepatic dysfunction and cerebral damage.

As an alternative to the theory that kernicterus resulted from the action of a toxin on the basal ganglia, Schmorl (1903) and Beneke (1907) both suggested that vascular damage caused by thrombosis or other change led to ischaemia of the nuclear masses and subsequently to pigmentation. Thorling (1922) also thought that ischaemia played a part and suggested a combination of low blood pressure and respiratory failure as the underlying cause. In the experimental field Spielmeyer (1930) found that the corpus striatum and cornu ammonis have a relatively poor blood supply and are liable to damage in disease affecting the latter. Meyer (1936) showed that the globus pallidus, inferior olives, dentate nuclei of the cerebellum, and cornu ammonis are the most commonly injured in anaemia of the brain, whether the latter was caused by morphine, carbon dioxide, or carbon monoxide poisoning. That asphyxia and anoxia affected these regions severely was also demonstrated by Wolff (1937) and by Putnam (1937). These findings were interpreted by various authors as indicating that some type of vascular damage was responsible for the changes in kernicterus. In a study of the blood-brain barrier, Broman (1941) decided that vascular injury was an essential preliminary before cerebral tissue could be induced to take up trypan blue. This latter dye had been shown by Friedemann (1942) to resemble the action of bilirubin. With the discovery of the Rh blood groups a great impetus was given to the study of the disease process, and many workers attempted to establish a relationship between vascular changes and the development of kernicterus. Diamond and Denton (1945) and Liber (1945) suggested that the terminal capillaries to the nuclear masses might become blocked by cellular debris resulting from haemolysis. Wiener (1946), in his theory concerning the pathogenesis of haemolytic disease, postulated the blocking of these terminal capillaries by agglutination thrombi with subsequent cell damage. Unfortunately as Levine (1946), Vaughan (1946), and Cappell (1947b) pointed out there is no histological evidence to support these theories. Recently Wiener and Gordon (1948) retracted the thrombosis hypothesis.

The discovery of the Rh blood groups explained the familial incidence of the disease which had puzzled so many previous investigators. It was then shown that the antibody in the mother's serum acted on the antigen of the infant's red cells causing haemolysis of the latter. This has led some authors to suggest that a direct antigen-antibody reaction occurs in kernicterus with the cerebral cells acting as the antigen. Yannet and Lieberman (1946) believe that this is a possibility, but there is no clear proof that such antigen is present in the cerebral neurones or that such a reaction occurs. Darrow (1938) had suggested that anaphylaxis might play a part in the aetiology of kernicterus. Recently, Darrow and Chapin (1947) have repeated the suggestions that in addition to the antigen-antibody reaction there is an anaphylactic process which accounts for the onset of icterus gravis and the development of kernicterus in some cases. Their explanation of the development of haemolytic disease is not a very convincing one.

Orth (1875) had suggested that there might be some congenital inferiority of the brain predisposing to the localization of bile in the nuclear masses. This suggestion has met with considerable support in recent years. Fitzgerald *et al.* (1939) believed that a degree of ' maldevelopment ' was a primary factor in the onset of kernicterus. Frolich and Mirsky (1942) produced convulsions in young rats but not in older ones by administration of bilirubin. Vaughan (1946) was inclined to believe that ' immaturity of cerebral and cerebrovascular tissue ' played a part in the aetiology of kernicterus. More recently, Lande (1948) thought that in some families the nervous system was more liable to toxic or emotional upset than in others, and quoted a few examples in support of her belief. It is not a simple matter to prove or disprove such a theory but no cases in the present series showed any evidence of cerebral immaturity.

The main difficulty in accepting one or other of the theories which have just been considered lies in the fact that the majority lack a sound histological basis for some of their premises. This may partly result from the lack of many detailed histological reports in the literature. Zimmerman and Yannet (1933; 1935) and Fitzgerald *et al.* (1939) have presented the most detailed reports of their cases, but histological data were only obtained in four instances. One of the first problems to be solved is whether the pigmentation of the cerebral masses is a primary occurrence or whether it is secondary to nerve cell injury. Zimmerman and Yannet (1933) state:

> ' Opinion is almost unanimous . . . that following some injury, the nerve cells are subsequently stained with the bile pigments carried to

them by the blood stream. This differs in no way from the well known fact that any intravital dye will localize in zones of injury, leaving unstained tissues which are not damaged.'

This is by far the most reasonable view, as Vaughan (1946) has remarked. The ganglion cells are almost certainly damaged in the first instance and thereafter assimilate bilirubin to a greater extent than the surrounding areas which are undamaged. If this assumption is correct, it is then necessary to decide what agent or agents are responsible for the original damage to the cell. In so doing, we must take into account (1) that kernicterus does not occur at birth but may occur within a short period of time following the onset of jaundice; and (2) that irreversible cellular damage did not appear to occur before the end of the first week of life in the present series of cases.

Yannet and Lieberman (1946) hold diametrically opposed views. They believe that cerebral injury is entirely secondary to the destruction of red blood cells during certain periods of foetal life. The resultant anoxaemia causes permanent injury to the developing neurone, and the cerebral damage is well established before birth. This belief is also supported by Parsons (1947). There seems to be no histological evidence to support this view. As Cappell (1947b) has remarked, if the neurones are damaged during foetal life it is remarkable that no histological evidence of neuroglial reaction to neuronal death is present in the brains of patients who die within the first day or two of life.

It will be remembered that several experimental workers, notably Spielmeyer (1930) and Meyer (1936), have shown that the areas involved in kernicterus are those most commonly injured by anaemia or by anoxia of the cerebral tissue. Thus it would seem most probable that the antigen-antibody reaction in the foetus results in the production of a sufficient degree of anaemia to cause cerebral anoxia. Vaughan (1946) pointed out that he was unable to correlate the degree of anaemia with the onset of kernicterus. The recent work of Mollison and Cutbush (1949) shows that some degree of anaemia is present in nearly all cases of icterus gravis resulting from haemolytic disease, but this anaemia may be concealed in the early stages. It would seem probable, therefore, that anoxia is responsible for the original cell damage which leads to subsequent pigmentation. This damage is of such a nature that the cell as a whole is not destroyed but is merely sufficiently changed to permit the bile-staining to occur. The oxygen lack is sufficiently severe to render the cell membrane unduly permeable to bilirubin but is not so great as to cause cell death. As Zimmerman and Yannet (1933) point out, groups of cells in the cerebral cortex, in the white matter around the lateral ventricles, and in the cerebellar cortex may show similar changes to those in areas more commonly affected. As the lesions are so very widespread they are most probably the result of anoxia.

Once pigmentation has occurred, the combination of anoxia and the presence of pigment in the cell eventually leads to the death of the cell. On histological grounds there is reason to believe that this process of gradual cell death occurs over the first week of extra-uterine life. It occurs first in the very vulnerable cornu ammonis and then in the other affected areas. After the death of the neurones the cerebral tissue undergoes necrosis with the formation of lipoid globules. These globules are then removed by the phagocytic action of the microglial cells and ultimately astrocytic replacement occurs with some shrinkage of the affected areas.

From a consideration of the manner in which kernicterus develops it is obvious that it is in the acute stage that therapy is likely to prove most useful. It is known that kernicterus can occur within 18 hours of birth, so if severe jaundice is present at birth treatment should be begun immediately. Since there are few reliable clinical criteria to indicate which patients are likely to develop kernicterus, all cases of severe icterus resulting from haemolytic disease should be treated within 12 hours of birth. Since the cerebral pigmentation would appear to result from anoxia, the obvious solution is to supply blood with full oxygen-carrying capacity, i.e. by the transfusion of Rh negative blood. Rh positive cells are quickly destroyed (Mollison, 1943) and so their beneficial oxygen-carrying power would soon be lost. Darrow and Chapin (1947), who have suggested an anaphylactic condition being responsible for the development of kernicterus, and Vaughan (1946) believe that better results are achieved by the use of Rh positive blood. This requires further confirmation and it would probably be wiser at present to use Rh negative blood. Whether the direct transfusion or exchange-replacement transfusion method is used will depend on the preferences of the clinician and the resources at his disposal. Wallerstein (1947) has suggested that if exchange-replacement therapy using Rh negative blood is begun immediately after birth kernicterus will not develop. Further work is necessary to substantiate his opinion. Whichever technique is used it must be emphasized that it must be instituted at the earliest possible moment in order to have any hope of success. Since the findings in the present series appear to indicate that irreversible

cytological change does not occur before the end of the first week, it may be worth while transfusing patients who were not examined until signs of cerebral irritation had become apparent. If the cerebral anoxia were overcome, further involvement of other nuclear masses might be prevented. By the time irreversible histological change has occurred and the process is fully established, there is no benefit to be derived from blood transfusion therapy. Treatment of this stage of the process should be confined to the prevention of secondary infection and to the care of the child's mental and physical development. Docter (1945) has observed that if great care is exercised with these unfortunate children a striking improvement may occur within the limits of their physical disability. Nevertheless, in spite of the early diagnosis of haemolytic disease and the institution of Rh negative blood transfusion therapy, the outlook in patients with kernicterus is not good. It is hoped that further improvements in methods of treatment in the early stages may achieve better results.

Recently, Yannet and Lieberman (1946) suggested that some cases of mental deficiency might be due to haemolytic disease. Cappell (1947b) discounts the evidence collected by Yannet and Lieberman, and does not believe that cases of idiopathic mental deficiency are the result of haemolytic disease. Cappell (1947b) has suggested, however, that the diffuse bile-staining of the cerebral cortex associated with an underlying kernicterus may cause mental deficiency in some instances. This diffuse bile-staining of the cortex is commonly found in patients with severe icterus who die in the neonatal period quite irrespective of the presence or absence of kernicterus. The incidence of such diffuse bile-staining is too frequent for it to be closely associated with the development of mental deficiency in later life.

If mental deficiency should result from the effects of haemolytic disease in infancy it is most likely to occur in the instances where there is deep icterus of groups of cortical cells. This has been described by Zimmerman and Yannet (1933), and some deep staining of the subcortical white matter was present in one case in this series.

Conclusions

From a study of the cases in this series it can be seen that nuclear jaundice is always associated with icterus gravis neonatorum resulting from haemolytic disease. It was not observed in any of the patients with hydrops foetalis or haemolytic anaemia nor has it been found in connexion with severe icterus other than that resulting from haemolytic disease. It was not present at birth in any case, but was found at necropsy in a patient who died 18 hours after birth. It would seem most probable that the antigen-antibody reaction in the foetus causing haemolysis of red cells results in a sufficient degree of anaemia to cause cerebral anoxia. This anoxia severely affects the cells of the nuclear masses, which are extremely sensitive to an anoxic state, and is sufficient to cause increased permeability of the cell to bilirubin but not to cause cell death. No evidence of cell death was found on histological examination of the brains of patients who died within a few days of birth. Cell death ultimately occurs, and is first observed in the cornu ammonis towards the end of the first week of life. Thereafter the affected nuclear masses undergo gradual astrocytic replacement and the typical neurological signs of the condition become apparent. Up to the present time the outlook in patients with kernicterus has been exceedingly grave. It is to be hoped that modern methods of transfusion therapy, if instituted soon after birth, will produce more satisfactory results. Once irreversible cytological change has occurred no specific therapy is of any avail. In such patients careful attention must be given to the prevention of secondary infection and to the promotion of maximum mental and physical activity within the limits of their disability.

Summary

The clinical and pathological features of 37 cases of nuclear jaundice occurring among 110 patients with severe icterus neonatorum are described.

Twenty-eight of these 37 patients died by the end of the first week of life. Only four survived the neonatal period, and only two are alive at the time of writing.

The histological changes present in the brain in nuclear jaundice are described in detail, and an attempt is made to explain the development of the condition on the basis of these histological findings.

The prognosis in nuclear jaundice is exceedingly grave both as to the immediate chances of survival and the future development of the affected child. It is too early to judge the effect of modern methods of transfusion therapy.

I wish to thank Dr. A. R. Macgregor and Prof. R. W. B. Ellis for much useful advice and encouragement. I am indebted to the clinical staffs of the Simpson Maternity Pavilion, Edinburgh, the Royal Hospital for Sick Children, Edinburgh, and the Elsie Inglis Memorial Maternity Hospital, Edinburgh, for access to their clinical records. The serological investigations were carried out by the staff of the Blood Transfusion Department, Royal Infirmary, Edinburgh, under the supervision of the Director, Dr. R. Cummings. The photomicrographs were produced by Mr. T. C. Dodds, of the Pathology Department, University of Edinburgh.

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HYPERTENSION OF RENAL ORIGIN IN CHILDHOOD

BY

A. L. GRIFFITHS, M.B., D.C.H.
From the Department of Child Health, University of Liverpool

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A persistently raised blood pressure is uncommon in children. Essential hypertension is rare, only a few cases having been recorded (Court, 1941). Endocrine causes, such as the hyperadrenalism of phaeochromocytomata (Snyder and Vick, 1947) are also uncommon. Elevation of the systolic pressure occurs in diseases of the heart and great vessels, being most notable in coarctation of the aorta and in severe degrees of aortic incompetence. The majority of cases of hypertension, however, are associated with renal disease.

It had been realized for many years that some connexion existed between renal disease and hypertension. Bright noted the cardiac hypertrophy of renal disease in 1838. How renal disease could affect the blood pressure was not apparent until Goldblatt *et al.* (1934) showed that in rabbits a pressor substance is liberated from kidneys to which the blood supply has been reduced. This work has since been developed and extended to other animals, and it is thought probable that the findings are applicable also to man, although this has not been proved conclusively.

Butler (1937) was the first to employ nephrectomy deliberately for the relief of hypertension in a child, although Quinby in 1923 found a fall of blood pressure in a case from which a diseased kidney had been removed. Since then many similar operations have been undertaken.

Recently Trueta *et al.* (1947) have put forward their views on the possible role of the kidney in essential hypertension and in the hypertension of chronic renal disease.

The experiments of Goldblatt *et al.* and their subsequent elaboration by others have shown the probable mode of production of hypertension in many cases in which there is an organic cause, whereas Trueta and his colleagues describe a possible mechanism in cases in which organic change is absent at the onset of hypertension and only develops later in the disease.

Cases Preceded by Organic Change

The cases in which there is apparent renal disease can be divided into the following three groups.

(1) The situation when there is obvious obstruction of the blood flow to the kidney by a lesion of the renal artery.

A case of partial occlusion of the renal artery by a muscle plug is described by Leadbetter and Burkland (1938), and an aneurysm of the renal artery occurred in the case described by Howard (1940). These are rare conditions but their importance lies in their close analogy with Goldblatt's experiments, showing that these can apply to the human as well as to the animal subject.

(2) Cases in which the lesions affect smaller vessels within the kidney substance, and probably only localized areas of the kidney become ischaemic.

In polyarteritis nodosa the characteristic lesions occur in the walls of the smaller arteries, producing either partial or complete thrombosis, or dilatation to form tiny aneurysms. Hypertension occurs in 64 per cent. of all cases according to Miller and Daley (1946), and was present in 30 per cent. of twenty-three cases in children reported by Rothstein and Welt (1933).

In amyloid disease the deposition of the hyaline substance in the walls of the arterioles and capillaries obviously restricts the blood flow, but there is, in addition, a second mechanism, which will be discussed later.

Chronic pyelonephritis is frequently found in cases of hypertension, and may be included in this group. Here the focal areas of fibrosis are thought to compress the renal vessels by their contraction as healing takes place. The disease may be unilateral, and nephrectomy for hypertension in these cases has been found to produce good results more often than in other types of unilateral renal disease (Langley and Platt, 1947).

Renal tuberculosis is a cause of hypertension in some cases. Possibly the disease acts by causing a thrombo-angiitis obliterans in the vessels which become involved in the spread of the lesions.

(3) In the third group tumours are present. They probably act by occupying space within the relatively rigid capsule, and, as they swell or grow, obstruct the venous return. This group includes cases of polycystic disease, renal neoplasms, and infarcts of the kidney.

Cases Without Early Organic Change

The work of Trueta and his colleagues (1947) provides a possible explanation for the cases in

which histological changes in the kidney do not appear until a later stage of the disease. They demonstrated a mechanism by which the blood supply to the renal cortex, and therefore the formation of urine, is regulated, and showed how overaction of this mechanism could produce cortical ischaemia. They applied these ideas to essential hypertension, suggesting that unknown stimuli, which might even be psychic in origin, caused prolonged overaction of this mechanism. This reduced blood flow to the cortex sufficiently to cause liberation of renin, yet not enough to impair renal function.

It is now apparent from the work in rats of Wilson and Byrom (1941) that one of the effects of prolonged hypertension is to produce arteriolar lesions. When this occurs in the renal vessels a vicious circle is completed. Narrowing of the vessels, which is now organic, leads to further ischaemia and liberation of renin, and the resulting hypertension causes further arterial lesions.

With reference to the hypertension of plumbism, Fishberg (1939) expresses the view that generalized arterial spasm is a major factor in the early stages before histological changes occur in the kidneys. He attributes this spasm to direct action of the lead on smooth muscle, and considers that the kidney plays no part. In view of the instability of the cortical arterioles demonstrated by Trueta *et al.* it seems likely that the kidney may after all play a part in raising the blood pressure to a higher level. Later, arteriosclerotic changes develop in the kidney and maintain the hypertension during the chronic stages of the disease.

In cases of chronic renal disease of various origins Trueta *et al.* have shown that prolonged use of the bypass through the medulla results in permanent dilatation of these pathways. This in turn leads to the formation of ' arteriae rectae verae ' running from arterial to venous sides of the medullary circulation, and permanently diverts blood from the cortex. The best example is amyloid disease, where the cortical circulation is mechanically obstructed by the hyaline deposits, and the bypass is forced to dilate.

The relationship between hypertension due to gross organic renal disease and that probably ascribable to vasospasm is intimate, and some examples may be regarded as borderline instances, for example, acute and chronic glomerulonephritis.

The most striking histological feature in the early stages of acute glomerulonephritis is the absence of blood from most of the glomerular capillaries, indicating gross diminution in blood flow; it is not surprising that hypertension frequently occurs. Although mechanical obstruction by endothelial thickening of the capillaries may be the cause of the ischaemia, Volhard (1931) suggests that vasospasm in the renal vessels is responsible.

In chronic glomerulonephritis also the histological picture of glomerular lesions and fibrous tissue replacement of the atrophic areas of parenchyma makes it easy to visualize reduced blood flow with resultant anoxia, liberation of renin, and hypertension.

It has been shown experimentally in dogs by Levy *et al.* (1937) that obstruction of the ureter causes a marked diminution of the blood-flow through the kidney, thus affording a possible explanation of the occurrence of hypertension in uncomplicated hydronephrosis.

Case Reports

Case 1. This child, Maureen McC., was admitted at the age of nine years with an acute exacerbation of a chronic pyelonephritis. She presented with haematuria and her blood pressure was 150/130 mm. Hg. Blood, pus, and Bact. coli were found in her urine. The right kidney was enlarged and easily palpable. The optic fundi showed some blurring of the discs, and a slight increase in light reflex from the arteries.

Previous illnesses included measles, pertussis, chicken-pox, mumps, and jaundice, and there had

FIG. 1.—Tracing of retrograde pyelogram showing a mild degree of bilateral hydronephrosis with dilatation of the ureters. (Case 1.)

been frequent attacks of tonsillitis for four years, the most recent being eight weeks previously. There were no relevant points in the family history.

A course of sulphanilamide temporarily sterilized the urine, but pyuria recurred a few days later and persisted. The blood urea varied between 39 and 46 mg. per cent. The blood pressure rose to 180/140 mm. Hg.

After six weeks she was transferred to a convalescent home where her urine continued to show

varying amounts of albumin, pus, and Bact. coli despite two further courses of sulphonamides. It was still infected on discharge nine months later. Although her general condition was much improved her blood pressure had risen to 210/150.

The child was readmitted at the age of twelve years with gross haematuria, actual clots being passed. Her general condition was good but her blood pressure was 255/230 mm. Hg. The urine was still infected. Blood urea now ranged between 48 and 75 mg. per cent. Pyelography showed a moderate degree of bilateral hydronephrosis with dilated ureters (fig. 1).

Gross haematuria occurred intermittently, and her blood pressure continued to rise. Exudates, haemorrhages, and sclerotic changes could be seen in the retinae. Her condition began to deteriorate rapidly. The blood pressure rose to over 300/150 mm. Hg. and bilateral detachment of the retinae occurred. Haematuria was so gross that a waxy pallor developed. Haemoglobin fell to 28 per cent. and the plasma proteins to 3·3 per cent. with an albumin:globulin ratio of 1:1. She developed uraemic symptoms as the blood urea rose to 204 mg. per cent., and a pericardial friction rub developed over the whole praecordium. Slight oedema of the face appeared, becoming more generalized later. Death occurred two months after her admission.

PATHOLOGY. The pericardial sac was seen to be covered with shaggy, blood-stained exudate and contained about 200 ml. of blood-stained fluid. There was generalized hypertrophy of the heart, especially of the left ventricle. Both kidneys were slightly enlarged and soft, and the capsule was adherent over areas of scarring. There were numerous small abscesses in the cortices. The cut surface was hyperaemic and oedematous, with scars of fibrous tissue and streaks of pus extending from medulla to cortex. The ureteric pelves were moderately dilated and inflamed containing purulent urine. There was slight dilatation of the ureters. The bladder also contained purulent urine, and its mucosa was inflamed. The para-aortic glands were enlarged.

HISTOLOGY. On histological examination the sections of the kidney showed areas of scarring in which most of the glomeruli had become hyalinized and others showed periglomerular fibrosis. The tubules were dilated and many contained hyaline eosinophilic material. Some of the tubules contained pus, almost forming small abscesses. Scattered areas of round cell infiltration could be seen. Vascular changes were present, consisting of hypertrophy of both media and adventitia of the arterioles, extending into the afferent arterioles of the glomeruli. There was intense congestion and round cell infiltration of the subepithelial layers of the ureteric pelvis.

The picture was that of chronic pyelonephritis, with superimposed acute pyelonephritis.

Case 2. This child, Clara J., aged thirteen years, was admitted with pains in her joints accompanied by haematuria of eleven days' duration. Two weeks before admission an abscess had appeared in her left axilla and had ruptured spontaneously. During the previous two years she had suffered with increasingly severe attacks of headache and vomiting and occasional attacks of abdominal pain. Previous illnesses included measles, chorea, and jaundice. There was nothing of note in the family history.

Examination showed a thin child, below normal height. There was tenderness in the left renal angle and along the line of the left ureter, and the kidney on that side was palpable. The urine showed gross

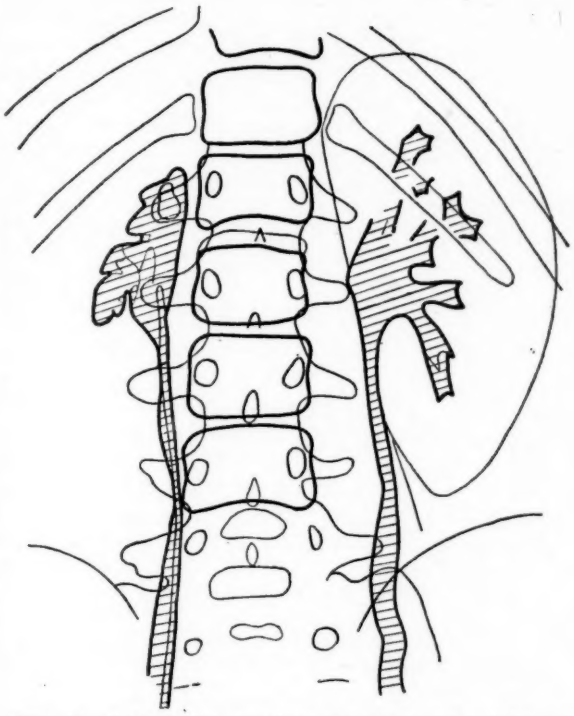

FIG. 2.—Composite tracing of retrograde right and excretory left pyelograms showing the blunting and bunching together of the calyces of the atrophic right kidney, and the hypertrophied left kidney. (Case 2.)

haematuria and albuminuria and a few leucocytes and Bact. coli were found. The blood urea was 31 mg. per cent. and the Wassermann reaction was negative. The blood pressure was found to be 270/215 mm. Hg. The retinae showed exudates and oedema to a marked degree with minute haemorrhages. The retinal arteries were narrowed and tortuous. Intravenous pyelography showed complete lack of excretion on the right side, but the left kidney appeared to be hypertrophied.

She continued to lose blood by haematuria, epistaxis, and finally, by a brisk haemorrhage into the bowel; her haemoglobin fell to 44 per cent.

At the same time her blood pressure fell, reaching 180/160 at the time of the rectal bleeding, but it rose again afterwards.

The child now began to complain of painful tingling sensations in her left arm, and a false aneurysm of the third part of the axillary artery rapidly developed and had to be ligatured off leaving an arm partly paralysed and with poor function. (Later this arm recovered almost completely.)

Retrograde pyelography was then performed and clearly outlined the right ureteric pelvis showing blunting and bunching together of the calyces (fig. 2). It was therefore decided to remove whatever might be remaining of this kidney, although the child had gradually lost weight and had become extremely emaciated.

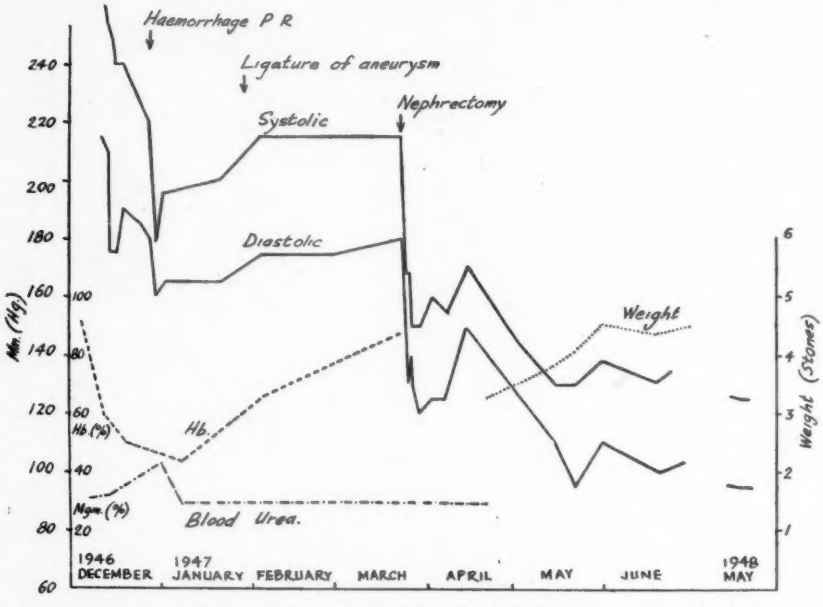

FIG. 3.—Graph showing the immediate fall in blood pressure which followed nephrectomy, and the subsequent continued improvement. (Case 2.)

At operation a small atrophic kidney was found and removed, and there was an immediate fall in blood pressure (fig. 3). There was also a rapid improvement in her general condition. Blood urea was 29 mg. per cent., and urea clearance 64 per cent. (standard).

It seems reasonable to assume from the patient's course during a long period of observation that she would soon have died if nephrectomy had not been performed. The eye changes showed that the hypertension had reached a malignant stage and there was no tendency for it to fall except temporarily following haemorrhages. The improvement which followed nephrectomy was most dramatic; the child became much brighter, her appetite returned, and emaciation rapidly decreased. She has now maintained this improvement for two years, and so far shows no return of the hypertension. Her eyes show interesting changes: the oedema of the retinae has subsided, but the central retinal arteries are protruding forwards on what seems to be the remains of some exudate. There are pinhead points of retinal atrophy with some pigmentation, probably due to resolved haemorrhages. Vision is: R. 6/6; L. 6/9. The fields of vision are normal.

PATHOLOGY. The right kidney measured $5\frac{1}{2} \times 2\frac{1}{2}$ cm. and consisted of a thin shell of tissue two to three mm. thick, surrounding dilated calyces. The kidney section showed practically no functioning renal parenchyma. The glomeruli were almost wholly hyalinized and some of the tubules were completely atrophied while others appeared to be open but were filled with hyaline eosinophil material. There was a marked interstitial fibrosis with infiltration of lymphoid elements. Subacute pyelitis was also apparent. The arteries and arterioles showed well marked hypertensive changes. The renal artery showed hypertrophy of the media, but no fibrosis. There was also a little proliferative endarteritis.

Case 3. This child, Peter B., aged thirteen years, presented with a severe epistaxis of three days' duration associated with a 'cold'. He had had similar attacks six months and one year before. Later a history was elicited of frequency of micturition for several years, but there was no definite history of pyelonephritis or nephritis. For the previous two years he had been suffering from headaches which were becoming more frequent. Chronic cough and a pale complexion had been noted since infancy. Previous illnesses included pertussis. There was nothing of note in the family history.

Examination revealed a very pale, anxious boy, small for his age. He was still bleeding postnasally but no local cause could be found. Bleeding continued for four days, but stopped after a blood transfusion had been given. Apart from a haemoglobin of 41 per cent. and red blood count of 2,060,000, blood investigations showed no abnormality. The blood pressure was found to be 220/130, but it fell as bleeding continued, rising again later.

The optic fundi showed slight oedema of the discs, accentuated light streak of the arteries generally, and irregular contractions of some of the vessels. These changes increased slightly during the period of observation, and a few small areas

of retinal exudate appeared to the nasal side of the right disc.

Repeated examination of the urine showed no abnormality except on one occasion when some albumin and a few hyaline casts were found. Nevertheless it was felt that the urinary system should be fully investigated. The blood urea varied between 34 and 45 mg. per cent. Blood calcium, phosphorus, and phosphatase were normal. Urea clearance (maximum) was 74 per cent. The urea concentration test was in the lower limits of normal, and the urine concentration test (Fishberg's modification) showed a maximum specific gravity of 1,016. Phenolsulphonephthalein excretion was 20·4 per cent. in the first hour, 16 per cent. in the second hour, and 2·5 per cent. in the third hour. These tests suggested impairment of renal function.

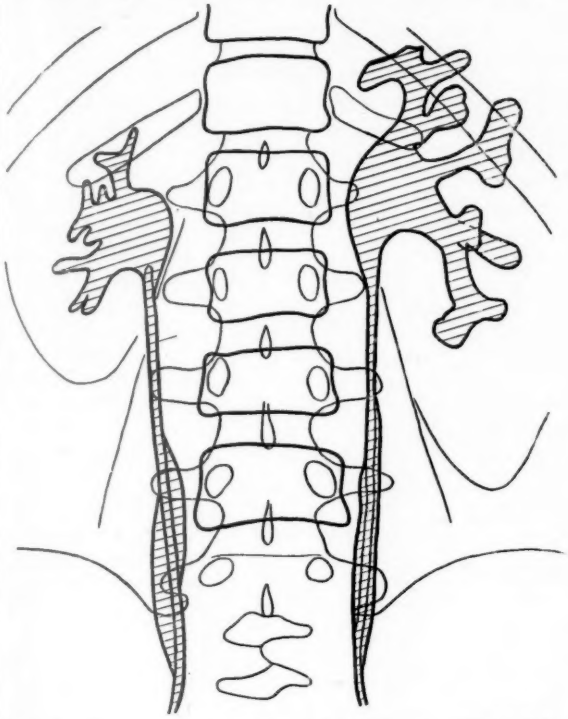

FIG. 4.—Tracing of retrograde pyelogram. (Case 3.)

Intravenous pyelograms showed a similar concentration of dye on both sides. The right kidney shadow appeared small and irregular, the calyces were deformed, and the ureter slightly dilated. The left kidney appeared to be uniformly enlarged with elongated calyces. Retrograde pyelograms confirmed the abnormal shape of these calyces (fig. 4). On injecting indigo-carmine intravenously during cystoscopy the dye appeared first at the left ureteric orifice in four minutes in high concentration, but it did not appear at the right ureteric orifice until three and a half minutes later and was in poor concentration.

The child's blood pressure had risen again to over 200/150 mm. Hg., the haemoglobin percentage was also rising, and attacks of headache had recurred, accompanied by vomiting. In view of these symptoms and the increase in the eye changes it appeared as though his hypertension had entered upon the malignant stage. After consultation it was decided to remove the right kidney.

At operation the peritoneum was opened to allow the left kidney to be palpated. It was large, firm, and smooth. The peritoneum was closed and the right kidney was removed.

There was an immediate fall in blood pressure which was not maintained (fig. 5). A year later the blood pressure was 230/140 mm. Hg. Symptoms, however, have been completely relieved and the child's general condition is much improved. There has been no increase in the blood urea, though the phenolsulphonephthalein excretion has fallen to 21·7 per cent. in two hours.

His fundi still show hypertensive changes, though there has been slight improvement. Fields of vision and colour vision are normal.

PATHOLOGY. The kidney measured 7×3·5×3 cm. and showed externally a number of grooves dividing it into three main portions. The capsule was thickened and adherent at these grooves and

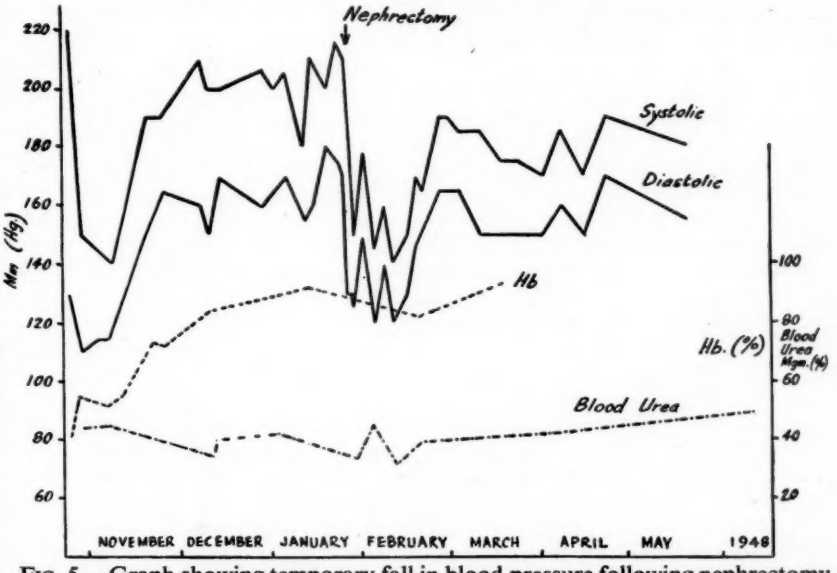

FIG. 5.—Graph showing temporary fall in blood pressure following nephrectomy. (Case 3.)

to a lesser extent elsewhere. One small cyst was present beneath the capsule at the lower pole. On section the cortico-medullary pattern was seen to be maintained on the whole in the upper and lower portions, but was less distinct in the central zone. The peripelvic fat was increased, with some haemorrhages at the lower end, probably due to operative trauma. Vessels at the cortico-medullary junction were congested and prominent.

Microscopic examination of the portion of muscle removed for section showed only a few small vessels whose appearance was normal. In the kidney the appearance of the upper and lower thirds was similar. The capsule was normal except over scanty areas of fibrosis where it was thickened. The glomeruli were normal, occasionally separated from the periphery of Bowman's capsule by albuminous fluid, which was also present in the moderately dilated tubules. The glomerular afferent arterioles were normal. There was no intertubular infiltration. There were a few, wedge-shaped areas of fibrosis, sharply defined from surrounding tissue, in which the glomeruli were hyalinized, the tubules atrophied and dilated, and interstitial tissue increased and infiltrated with small round cells. There was a moderate degree of hyperplasia of the media of medium sized arteries, with musculo-elastic hyperplasia of the intima, but without gross narrowing of the vessels. In the middle zone of the kidney changes were similar, but there was more distortion of pattern by a greater number of zones of fibrosis. The appearance was that of the late result of pyelonephritis.

Case 4. This child, William N., aged three years and eight months, was admitted to the Royal Liverpool Children's Hospital with a subarachnoid haemorrhage of spontaneous onset. Since the age of eleven months he had had attacks of vomiting, preceded by headaches and lasting two to five days; they occurred at intervals of one to four months. The onset of the subarachnoid haemorrhage was about four days after the beginning of one of these attacks when he complained of unusually severe parietal headache and was more drowsy than normal.

Previous illnesses included two attacks of bronchitis during the year before admission to hospital, and tonsillitis three weeks before. He had not had any of the infectious diseases, and was not considered to have suffered from any kidney disease, although pus and albumin had been found in his urine seven weeks before admission.

On examination there was marked neck rigidity and Kernig's sign was positive. The optic fundi were normal. The heart sounds were loud and forceful and there was accentuation of the aortic second sound. Some cardiac hypertrophy was present, and a blood pressure of 210/170 mm. Hg. was noted. Lumbar puncture showed a xanthochromic fluid under a pressure of 280 mm. of cerebrospinal fluid, containing protein to an extent of 100 mg. per cent. and numbers of red blood cells. The urine contained albumin and pus cells. Blood urea was 25 mg. per cent. at first, but rose later. The Wassermann reaction and Mantoux tests were negative.

Neck rigidity and headaches subsided following a period of complete rest, but the blood pressure remained at a high level.

Intravenous pyelography revealed a normal left kidney, but there was no excretion of the dye on the right side. Retrograde pyelography showed the presence of a normal-looking pelvis on the right side, but intravenous indigo carmine was not excreted from this side (fig. 6).

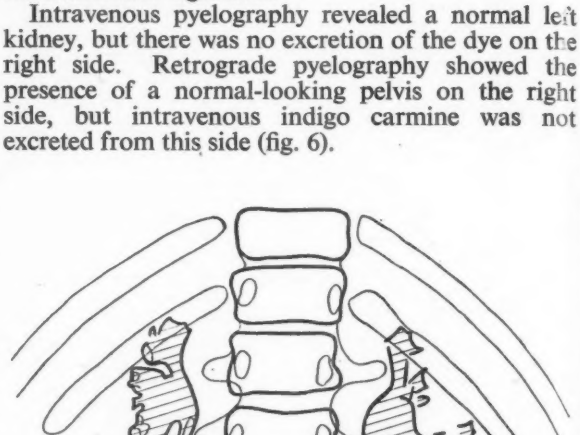

FIG. 6.—Composite tracing of retrograde right and excretory left pyelograms. (Case 4.)

It was decided to remove the useless right kidney.

The day before operation the blood pressure rose to 260/190 mm. Hg. and vomiting occurred, and on the day of operation the systolic pressure was even higher and could not be recorded. Clamping of the renal artery was followed by an immediate fall in blood pressure.

Following operation there was a rapid improvement in the boy's general condition. The decline in blood pressure (fig. 7) has been maintained, but it is not possible to say whether the improvement will continue. Eight months after operation his systolic pressure is 120 mm. Hg. He still has attacks of cyclical vomiting.

PATHOLOGY. No abnormality was found in the kidney either macroscopically or on microscopic

examination. It is interesting to speculate on the possibility of some form of stenosis or partial occlusion of the renal artery having been present, but there was no actual evidence.

Discussion

It seems reasonable to assume that in the first three cases the initial lesion was pyelonephritis which became chronic and resulted in progressive renal damage and gross scarring. The inflammation was still very active at death in case 1. In case 2 the infection had almost died out on the grossly damaged side, but the second kidney was becoming involved. In case 3 the disease was temporarily inactive.

Diagnosis. Absence of pus or albumin in the urine of a case of hypertension does not exclude renal disease as found in case 3 nor does a normal blood urea as in case 2 in which there was total loss of function of one kidney. The most valuable aid to diagnosis is the excretory pyelogram which should be obtained in all cases of hypertension in childhood. The result must be interpreted with caution since temporary obstruction of the ureter by clots of pus may prevent excretion of the dye. Moreover, complete absence of one kidney is by no means rare, seven such cases having been found in the Alder Hey Children's Hospital in two and a half years. Hydronephrosis of the single kidney was confirmed in three cases, and the presence of hypertension was established by the resultant post-mortem cardiac hypertrophy in two of them. Retrograde pyelography is essential to distinguish between a non-functioning kidney and its complete absence. Cystoscopy alone is insufficient as a ureteric orifice may be present in spite of the absence of the kidney on that side. Intravenous injection of indigo carmine during cystoscopy may be of help in determining which kidney is more affected. This was invaluable in case 3, where both kidneys appeared to be abnormal on x-ray examination.

None of these cases showed any evidence of obstruction in the urinary tract, nor of congenital malformation which would predispose to stasis and maintenance of infection, but all had foci of infection elsewhere. In case 1 the tonsils were unhealthy, and the child had been having frequent sore throats since the age of five. Case 2 had a chronic vaginal discharge at the age of four, and at present has chronic sinusitis. Case 3 has a chronic lung infection. The association of these foci and the hypertension is probably indirect, but they may possibly have served as the source from which the infection in the kidney originated, or was maintained and renewed.

Effect upon growth. In all these cases there was interference with growth. In case 1 weight was about normal for a child of nine and a half years, namely 62½ lb., although even then her blood pressure had risen to 180/140 mm. Hg. At the time of her second admission to hospital her weight had risen to 67 lb. only, a gain of under five pounds in two and a half years. Unfortunately her height was not recorded.

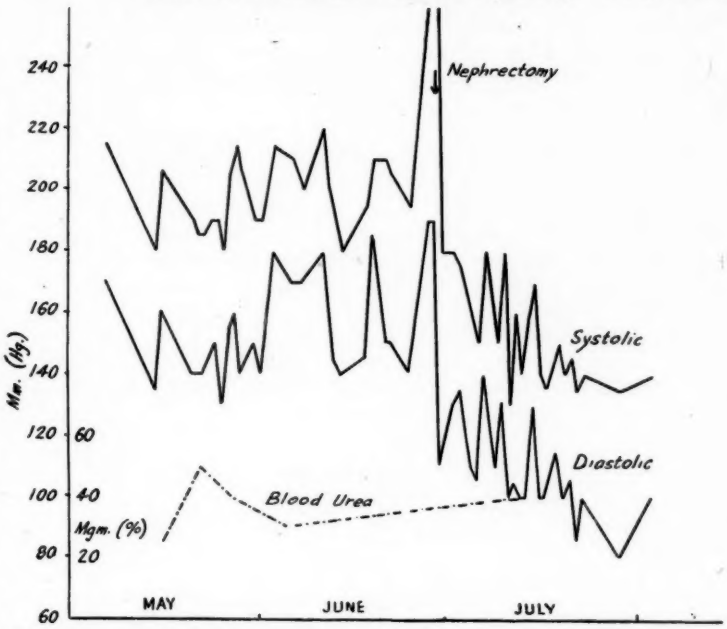

FIG. 7.—Graph showing the fall in blood pressure which followed nephrectomy. (Case 4.)

In case 2 there was gross emaciation. The lowest weight recorded was 45 lb. at the age of thirteen years, her height being 51 in. This was 9¼ in. below the average for her age. Over the past year her weight has steadily improved, and she now weighs 84 lb., still 30¾ lb. below normal. Her height is now 57 in., a gain of 6 in. in thirteen months.

Case 3 had a weight of 78 lb. and height of 56 in. before operation, 35 lb. and 8¼ in. respectively below normal. Five months later, although his blood pressure was still high he was clinically very well and had gained 5½ lb. and almost an inch in height. These figures for height and weight by no means qualify for the description renal dwarfism, being on the low side of normal extremes, but they do suggest a certain retardation of growth, probably occurring in the last year or two.

Prognosis. Complete success in the treatment of hypertension by nephrectomy can only be anticipated in the presence of one normal or only slightly damaged kidney. If both are affected there may be slight improvement as in case 3, and operation is perhaps justified, but if there is one good kidney a successful result may be obtained, even in the presence of a hypertension of over 200/160 mm. Hg of long duration and showing gross retinopathy.

Summary

The possible etiology of hypertension in cases of renal origin is briefly discussed.

Four cases of severe hypertension in children are described. One case is cured and one slightly improved following nephrectomy. Another case appears to be cured, but has not yet been followed up for a sufficiently long period.

Thanks are due to Professor Capon for his personal interest and encouragement in the preparation of this paper, to Dr. W. E. Crosbie, medical superintendent, Alder Hey Hospital, and to Miss I. Forshall for permission to publish the first three cases. I am indebted to Dr. J. D. Hay for permission to use one of his cases from the Royal Liverpool Children's Hospital.

The paper was prepared during the tenure of a 'Cow and Gate' scholarship in the Department of Child Health, University of Liverpool.

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EPULIS IN THE NEWBORN

BY

F. A. LANGLEY and J. DAVSON
From the Departments of Obstetrics and Gynaecology and of Pathology at the Victoria University of Manchester

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Epulis in the newborn is a comparatively rare condition and, although such tumours have been reported in the American and continental journals, the only reference in the British literature is that given by Willis (1948), who, discussing the status of 'myoblastoma', refers to papers by Ceelen (1931), Meyer (1932), and Crane and Tremblay (1945), describing cases of congenital epulis.

Case Reports

Case 1. K.G. was a female infant who, at birth, was found to have a small mass attached to the left lower alveolar margin by a narrow neck. Ten days later the rounded solid mass, measuring approximately 1 cm. in diameter, was removed, and when sectioned it was pale and firm.

HISTOLOGY. Much of the outer surface of the tumour was covered with squamous epithelium, but in one part this had been lost by ulceration and replaced by fibrinous exudate. Where the epithelium was intact the tumour cells lay closely beneath but were clearly separated from the basal epithelium (fig. 1). The tumour cells were large and mainly polyhedral in shape measuring up to 36μ; others were more elongated and very occasionally spindle-cell in shape. The more or less centrally placed nuclei were slightly oval, measuring 6-10μ, with well defined nuclear membranes. No mitoses were seen. The cytoplasm of the cells was filled with fine acidophile granules having no special arrangement so that the cells somewhat resembled xanthoma cells (fig. 2); but Sudan stains on frozen sections failed to demonstrate the presence of lipoid. The cytoplasmic granules stained blue with Heidenhain's azan and faintly pink with muci-carmine. Sections stained by Gömöri's silver technique showed that the cytoplasm contained fine granules sometimes arranged as rods, at other times as circles (fig. 4), and also that each cell was surrounded by a distinct reticulin framework (figs. 3 and 4).

In sections stained by Heidenhain's iron haematoxylin to demonstrate myofibrils it was found that the cytoplasmic granules failed to retain the stain after normal differentiation, and no longitudinal or cross-striated myofibrils could be demonstrated.

Case 2. This baby, C.V., was admitted to the Duchess of York Hospital for Babies, Manchester, at the age of two days, having had a normal delivery at full term; the birth weight was 7¾ lb. On admission she was seen to be a normal-looking, healthy baby apart from two pedunculated tumours arising from the upper alveolus to the left of the mid-line. The anterior tumour measured 4 cm. by 1 cm. and the posterior one 1·2 cm. by 0·8 cm. No other abnormality was found. The tumours were removed under local anaesthesia at the age of four days. The tumours were firm in consistency and the cut surfaces were uniformly grey. The child was discharged two days later and made a straightforward recovery. She was seen in the out-patient department at the age of three and a half months; at this time radiographs of the long bones and skull were taken but no abnormality was found. This investigation was made because at this time the true nature of the tumour was not understood and on account of the histological picture a diagnosis of multiple xanthomatosis was considered possible. The child was seen again at nine months of age; her weight was 24 lb. 8 oz. and she had infantile eczema. She was seen for the last time one month later when the eczema was still present. There was no recurrence of the tumour.

HISTOLOGY. The outer surface of the tumour was covered with squamous epithelium. This was separated from the tumour by a thin zone of connective tissue from which coarse strands descended into the substance of the tumour. No true lobulation was produced but these coarse strands broke up into fine fibres which surrounded each tumour cell. This pericellular reticulum was readily seen in the silver-stained preparations. The cells of the tumour were identical in morphology with those in Case 1.

Case 3. This child, H.M.S., was brought to the out-patient department of the Duchess of York Hospital, Manchester, at the age of five days. A pedunculated lump, about the size of a large pea, arose from the central position in the upper jaw. Next day this lump was removed under local anaesthesia in the out-patient department. The baby has been seen subsequently at four and six months of age. There is no sign of local recurrence of the tumour, and, apart from being slightly over-fat, she is in excellent health.

HISTOLOGY. About half of the surface of the tumour was covered by squamous epithelium; over the remainder of the surface the epithelium

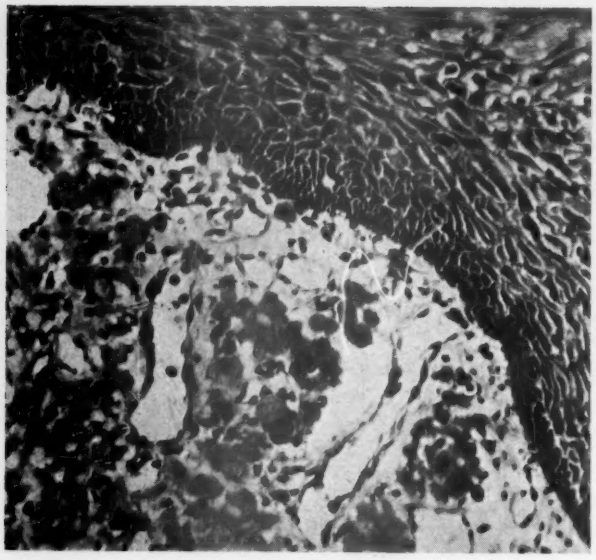

FIG. 1.—The tumour cells can be seen lying below the basal layer of the buccal epithelium; stained with haemalum and eosin. ×200.

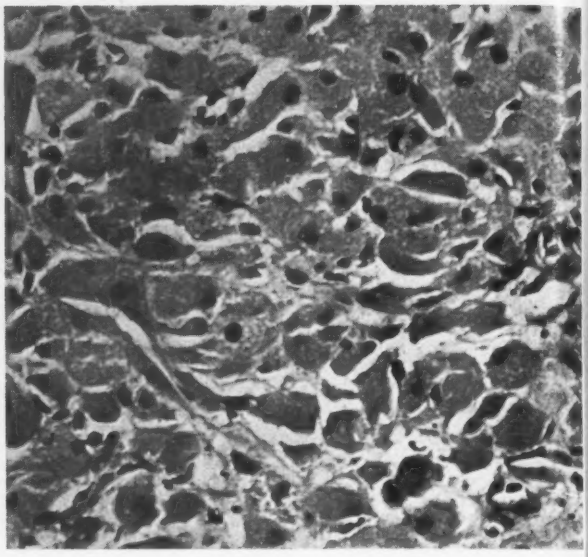

FIG. 2.—The tumour cells show some variation in shape, and contain abundant granular cytoplasm; stained with haemalum and eosin. ×290.

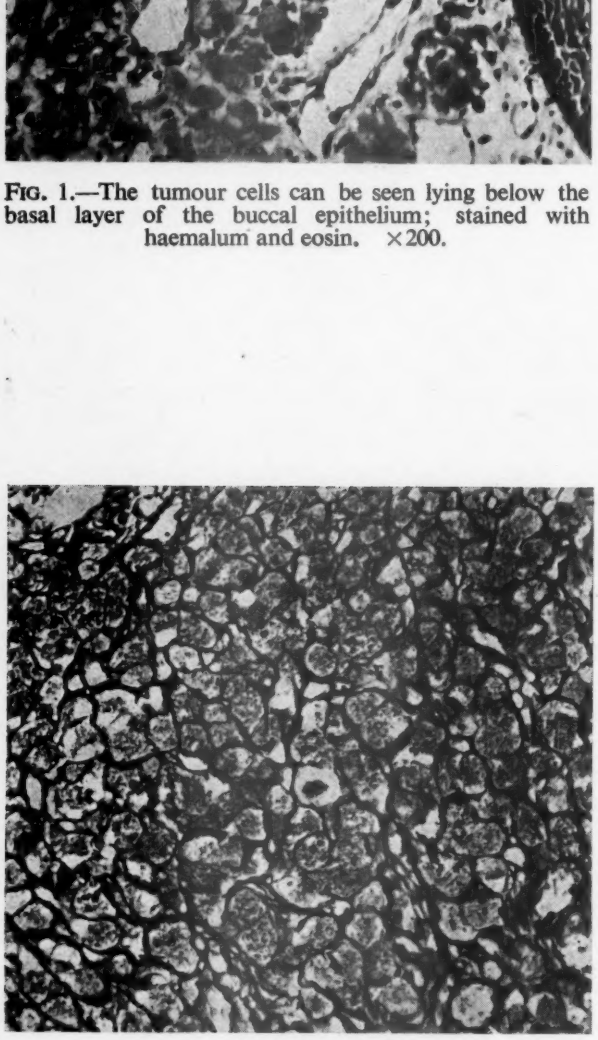

FIG. 3.—A silver impregnation stain shows that each cell is surrounded by a reticulin fibre mesh; stained with Gömöri's reticulin stain. ×200.

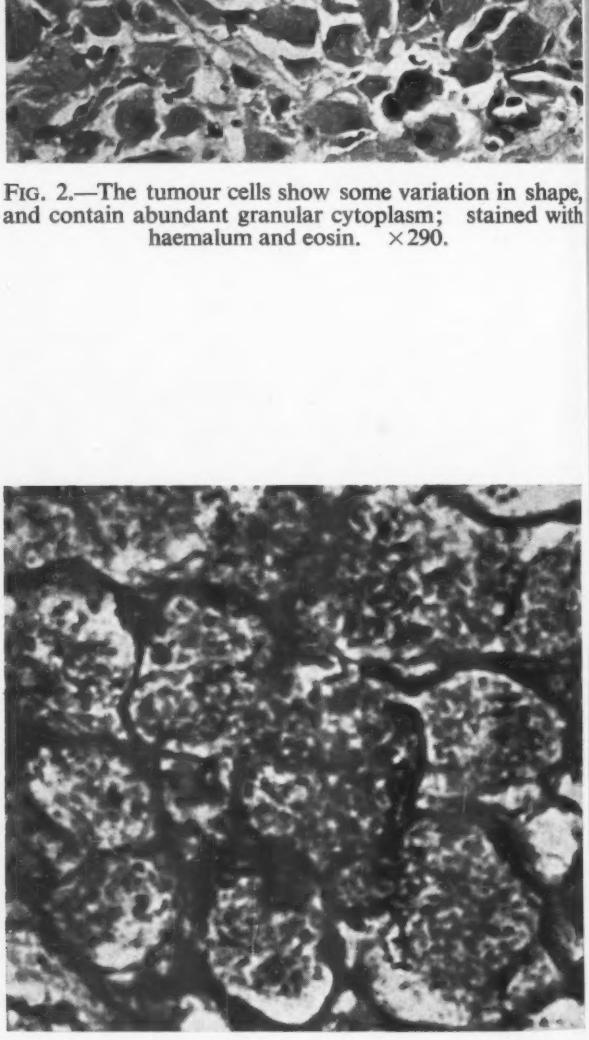

FIG. 4.—A higher magnification showing the numerous argyrophilic granules in the cytoplasm of the cells; stained with Gömöri's reticulin stain. ×800.

had been lost and replaced by fibrinous exudate. The body of the tumour was separated from the epithelium by a thin zone of connective tissue into which the inflammatory process extended. The cells of the tumour showed identical appearances with those of Cases 1 and 2.

Discussion

The three neoplasms occurring in the jaws of newborn infants showed identical morphological characteristics. The tumours were unencapsulated and the cells lay beneath and distinct from the overlying buccal epithelium. The tumour cells were large and polyhedral with central, rather dark, nuclei, and the cytoplasm was packed with fine, somewhat eosinophilic, granules. The cells thus had a superficial resemblance to xanthoma cells. Each cell was separated from its neighbour by a network of reticulin fibres. No lipoid was present in the tumour cells. The cytoplasmic granules stained blue with Heidenhain's azan and faintly pink with muci-carmine. No myofibrils were present. Similar tumours have been found attached to the maxilla by Massin (1894), Füth (1902), Kleine (1929), Volkmann (1929), Ceelen (1931), Meyer (1932), Leroux and Delarue (1939), Kratochovil (1941), Lascano-Gonzalez (1941), and Crane and Tremblay (1945), and to the mandible by Olivier (1895), Schorr (1906), Abrikossoff (1931), Jorge *et al.* (1932), and Crane and Tremblay (1945). The age distribution of patients with these tumours is interesting; of fifteen maxillary tumours (including ours) all except one was found in the first few days of life, but Kratochovil (1941) does not give the age of his patient. Of the eight mandibular tumours six were found in the first few days of life, one of Abrikossoff's (1931) cases was aged 36 years, and the other 55 years. Of the eleven cases of maxillary tumour whose sex is given, ten were female, and of the eight cases of mandibular tumour all, except Abrikossoff's two, were female. The three cases reported here were all female infants. Thus of twenty-two cases reported to date, in which the sex is known, nineteen were females.

Judged by the subsequent history, these tumours are benign; no recurrence was found after six months in Kleine's first case or after a year and a half in his second case. Massin's was well after one year and no recurrence was found after two years by Olivier (1895), Füth (1902), and Meyer (1932), and of three years by Jorge *et al.* (1932). Crane and Tremblay (1945) found no recurrence in their first case, and we found none in our three cases. This is in agreement with the general histological uniformity of the tumour cells and the absence of mitoses.

Origin of the tumours. Three main theories have been proposed to account for the origin of this type of tumour. It has been suggested that they may arise from muscle, misplaced dental anlage, or basal epithelium.

Tumours composed of cells similar to those found in congenital epulides have been found in the tongue by Abrikossoff (1926). Crane and Tremblay (1945) quote fifty-eight other cases, and Willis (1948) shows illustrations of two. In some, but not all, such tumours of the tongue, some cells show longitudinal and cross striations and transitions to undoubted muscle fibres. Similar cells have been found in muscle tumours in other sites, e.g. in the arm (Geschickter and Maseritz, 1939). Such tumours have therefore been classed as 'myoblastomas' by Abrikossoff (1926, 1931) and by Crane and Tremblay (1945), although the latter felt that no definite conclusion as to their myoblast origin could be drawn. In the early stages of muscle development in the embryo there is a phase when the myoblasts contain numerous cytoplasmic granules (Goldewski, 1902; Weed, 1936), and it is from these granules that myofibrils are thought to develop. The granular cells of the lingual 'myoblastomas' are considered to be homologous to these embryonic myoblasts. However, as Willis (1948) points out, true myoblasts of the embryo do not at any stage resemble Abrikossoff's 'myoblasts'; the granular cytoplasm and situation of the tumour cells suggests merely a superficial similarity. Willis also remarks on the similarity between these granular cells and the regeneration sprouts described by Clark (1946) in damaged muscle; hence, he suggests, the granular cell 'myoblastomas' of the tongue and other tissues are not neoplastic but degenerative or regenerative lesions of muscle fibres. Abrikossoff himself, in 1931, suggested that some 'myoblastomas' are derived from damage to muscle and that others are embryonic in origin. The absence of muscle from the sites of these epulides in the newborn renders their origin from degenerative or regenerative changes in muscle very unlikely. Further, the striking uniformity in histological structure of these epulides and the absence of muscle-like elements makes it probable that they may not be of the same nature as the lingual tumours.

The theory that these tumours are developed from misplaced dental anlage was proposed by Massin (1894). Kleine (1929) has examined this theory and rejected it. Attractive as the theory is, we have been unable to see any resemblance between the cells of the tumour and those of dental rudiments. Kleine (1929) himself proposed the view that these tumours arise from the basal epithelium of the oral cavity possessing embryonic potency. We have been unable to find evidence to support this view. The tumour cells lie clearly separated from the overlying basal epithelium in all three cases, and the fact that each cell is separated from its neighbour by a reticulin fibre mesh further argues against the epithelial origin of these tumours.

The tinctorial properties of the granules in the tumour cells are interesting but do not throw much light on the origin of the tumour. Schorr (1906) reported that, after fixation in alcohol, the granules stained red with eosin, yellow with picric acid, and

violet with polychrome methylene blue and thionin. Kleine (1929) in his first case found that the granules stained partly blue and partly red with muci-carmine, and with Heidenhain's azan they stained distinctly blue. This he took as evidence that the granules were mucoid. In our cases the granules had similar tinctorial properties. Since, however, mucoid granules can occur in both epithelial and connective tissue cells, these staining reactions cannot be taken to indicate the epithelial nature of the tumours, and as the individual cells are surrounded by a fine reticulum, it is more likely that they are mesenchymal.

Jorge *et al.* (1932) called their three tumours 'angiolinfangioma xantelomatosa'. They stressed the vascularity of their tumours, which was not a conspicuous feature of the other congenital epulides described in the literature. Moreover, although no specific stains for fat were used, their description suggests that fat was present in the tumour cells. It seems possible that the epulides of Jorge et al. (1932) are different from the others of this group, but the cells of many of these tumours give an impression of a xanthomatous nature on first examination.

In conclusion we admit that we have been unable to contribute any further positive evidence towards elucidating the histogenesis of congenital epulis, but recognize that clinically and morphologically these neoplasms constitute a distinctive entity. There appears no definite justification for calling these tumours myoblastomas, and we suggest that the term 'congenital epulis' be retained until further evidence of their histogenesis is forthcoming.

Summary

Congenital epulides in three infants are described. The tumours consisted of large round or polyhedral granular cells separated from each other by a fine reticulum.

The twenty-three similar tumours previously described are briefly reviewed.

The theories of origin of these tumours, namely muscular, misplaced dental anlage, basal epithelium, and lymphatic endothelium, are briefly discussed. None appears to be adequate.

It is suggested that these congenital granular epulides are mesenchymal in nature.

We wish to thank Professor S. L. Baker for helpful criticism, and Mr. F. Ward for the microphotographs.

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LETTERER-SIWE DISEASE

BY

A. A. MACKELVIE, F.R.C.S.Ed., and W. WALLACE PARK*, M.B.
From the Stirling Royal Infirmary and the Royal College of Physicians Laboratory, Edinburgh

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The term Letterer-Siwe disease was applied by Abt and Denenholz (1936) to a condition first described in detail by Letterer (1924) and later recognized by Siwe (1933) as a well defined clinico-pathological syndrome.

Letterer-Siwe disease is an illness of infants, almost invariably fatal, and of unknown aetiology. The main clinical features are an age incidence from two months to two years; an indefinite onset with no specific symptomatology; a febrile course lasting for a few weeks or a few months to death; generalized enlargement of the lymph nodes, enlargement of the spleen, and often of the liver as well; a haemorrhagic tendency, commonly producing a purpuric or ecchymotic skin rash most marked shortly before death; hypochromic anaemia, sometimes severe; destructive lesions in bone, commonly in the skull, rarely, if ever, in the bones of the hands and feet, but often occurring elsewhere in the skeleton, e.g. in the ribs, pelvis, humerus, femur, and may be clinically silent or associated with pain and tenderness, with or without overlying soft tissue swelling; sometimes mottling of the lung fields on x-ray examination; less commonly, secondary bacterial infection, such as otitis media or angina of the throat, and leucocytosis; no apparent hereditary or familial incidence. The characteristic pathological feature is excessive hyperplasia of the reticulo-endothelial tissue throughout the body, particularly in the spleen, lymph nodes, and skin.

Of the nine patients with Letterer-Siwe disease whose case-reports were analysed by Abt and Denenholz (1936), all had splenomegaly, a petechial and ecchymotic skin eruption, a moderate continued fever, and moderate to severe secondary anaemia, and all but one showed enlargement of the lymph nodes. There were alterations in the bone marrow cytology in eight of the patients (no details given in the remaining case) mainly in the form of proliferation of large, pale, histiocytic cells. Four of the patients showed lesions in bone.

The most helpful factor in reaching a correct diagnosis would be the knowledge that such a recognized syndrome existed. Biopsy of tissue from the spleen, bone marrow, or of a lymph node has been mentioned as a possible aid to diagnosis. To judge from reported cases, and certainly from the findings in our own case, the histological picture is not so specific that Letterer-Siwe disease can be diagnosed outright from biopsy. A biopsy of the three tissues could indicate reticulum cell overgrowth, and to that extent confirm a clinical diagnosis of Letterer-Siwe disease, but biopsy of a lymph node would probably always be the most useful. Much more than biopsy of the spleen or bone marrow it offers to the pathologist the chance of being able to exclude some of the other conditions which may cause generalized lymph node enlargement.

Conditions which have been mentioned as entering into the differential diagnosis include aleukaemic leukaemia, Hodgkin's disease and lymphosarcoma, generalized osteitis fibrosa, a local bone neoplasm or a metastasizing neoplasm with spread to bones, tuberculous disease of bone, myelomatosis, generalized xanthomatosis, 'von Jaksch's anaemia', and typhoid fever.

Since the article by Abt and Denenholz at least five other examples of the Letterer-Siwe disease complex have been described by Freud, Grossman, and Dragutsky (1941), Wallgren (1940) two cases, Gross and Jacox (1942), Jaffe and Lichtenstein (1944). This makes a total of 14 so far reported, but it is quite clear that many other examples were reported earlier under different names, for instance non-lipoid histiocytosis, reticulo-endotheliosis, or aleukaemic reticulosis, before their identity was realized. The name given to the disease by Oberling and Guérin (1934), 'acute reticulosis of infants,' is in many ways preferable to its present eponymous title. Letterer-Siwe disease is now considered to be only one variant of a basic granulomatoid disorder which appears on other occasions as 'infective' reticulo-endotheliosis, Hand - Schüller - Christian disease, and eosinophilic granuloma of bone. Transitional stages between these more distinctive forms of the disorder are relatively common. Jaffe and Lichtenstein (1944), for example, considered that the case described by Hand, which led to the association of his name with those of Schüller and Christian in the name Hand-Schüller-Christian disease, was more probably an example of Letterer-Siwe disease.

* Working with a grant from the British Empire Cancer Campaign.

Amongst the nine cases accepted by Abt and Denenholz as examples of Letterer-Siwe disease was one of a series of four (Case No. 4) described by Gittins (1933) in his study of 'Anaemia and Reticulo-Endotheliosis.' Apart from this we have not found any examples of Letterer-Siwe disease reported in the British literature, and our case report appears to be the first account in this country of Letterer-Siwe disease since the disease was recognized as a clinico-pathological entity.

Case Report

Baby A.W., a girl, aged 7 months, was seen on June 3, 1947, at the Outpatient Department of Stirling Royal Infirmary. Except for a history of possible whooping cough at the age of 14 weeks, the child had had no illness until four weeks before, when a swelling appeared behind the left ear. This swelling had been incised and treated as an abscess two weeks previously at another hospital where an otologist had reported that there was no middle-ear or mastoid disease. Three weeks before being seen at Stirling the child had developed a rash on the anterior thoracic and abdominal walls. She was fretful and was not gaining weight. There was no apparent pain and no history of diarrhoea.

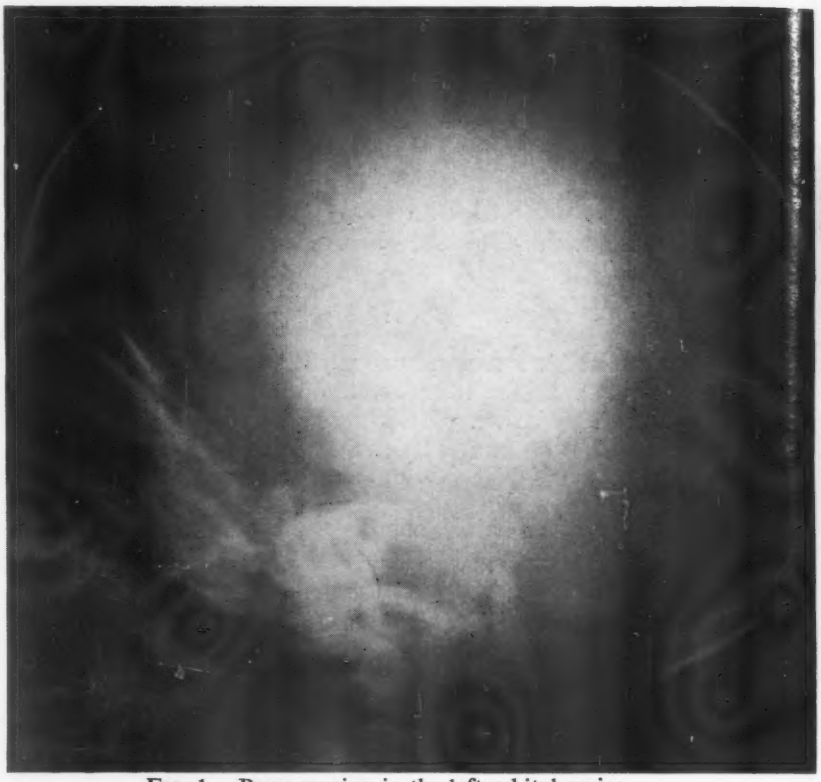

FIG. 1.—Bone erosion in the left orbital region.

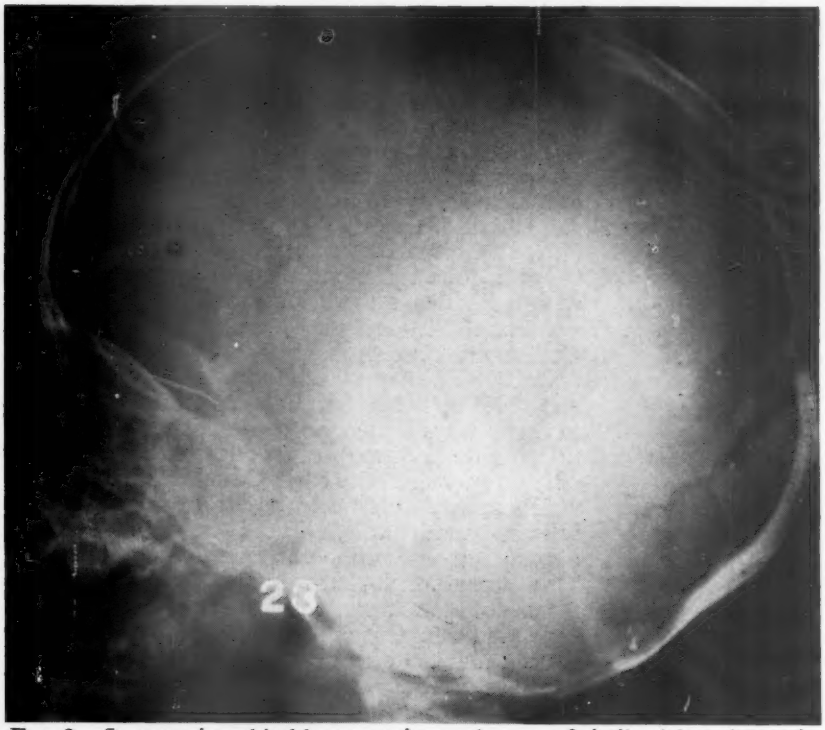

FIG. 2.—Increase in orbital bone erosion and areas of similar bone change in the occipito-parietal area.

Examination showed a pale child with a soft swelling, not red but tender, above the left mastoid area. Over the swelling was a small healed incision. The left upper cervical lymph nodes were slightly enlarged. No other lymph node enlargement was found, nor any enlargement of the liver or spleen. Over the anterior aspect of the lower thorax and upper abdomen there was a scaly, macular, petechial rash. The Wassermann reaction was negative, as was that of both parents. X-ray examination of

the left mastoid area showed no bone abnormality, but the plates were not very satisfactory.

The child was admitted to hospital on June 7, 1947. It was then found that a small firm swelling had developed in the upper outer area of the left orbit. X-ray plates showed an area of bone erosion (Fig. 1).

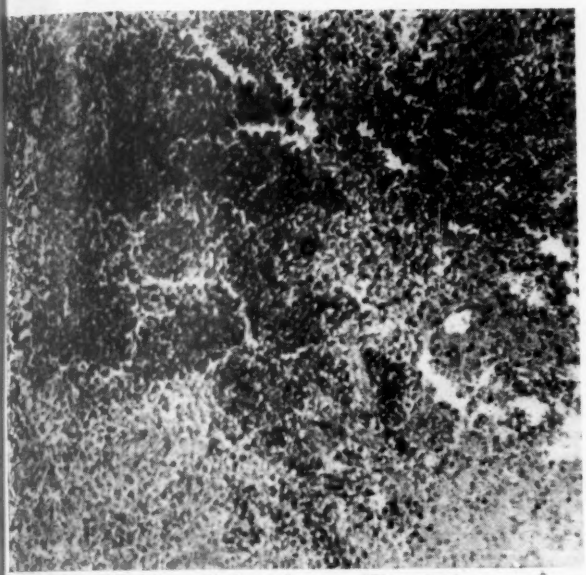

FIG. 3.—Highly cellular tissue. The dark areas are dense collections of eosinophil leucocytes. ×80.

On June 21, 1947, the mastoid swelling was opened, and the soft, greyish tissue curetted out was sent for pathological examination.

This first biopsy specimen was received at the Royal College of Physicians Laboratory, Edinburgh, a few days later. It consisted of three small fragments of soft grey tissue. Microscopically the tissue was highly cellular and without trace of organized anatomical structure. There was a background of moderately small, uniform cells, sometimes in loose masses, sometimes forming cellular sheets, and much extravasated blood. Here and there were small, well defined blood vessels. The tissue was widely infiltrated with polymorphonuclear leucocytes of which many were eosinophils. There were also many lymphocytes, a few plasma cells, and an occasional non-specific multinucleated giant cell. The appearances were not diagnostic and indicated a subacute or chronic inflammatory process with some patchy fibroblastic activity. On this occasion no special significance was attached to the eosinophil leucocytes.

Penicillin (50,000 units three-hourly) therapy was begun on June 23. The swelling above the left eye was larger. By July 10 the mass behind the ear was somewhat smaller, but an abscess had appeared in the neck below the ear. Penicillin (3,900,000 units) had been given.

On July 17 it was noted that the swelling in the left orbit had increased greatly, was fluctuant, and was causing strabismus. X-ray examination showed an increase in the area of bone erosion (Fig. 2). Two days later the orbital swelling was curetted, and a specimen of similar soft grey tissue with small yellow and red areas was again sent for examination.

This second biopsy specimen consisted of many small irregular fragments of soft tissue and, as in the first specimen, microscopic examination showed a mass of highly cellular, haemorrhagic tissue but there were three main differences: (*a*) The predominant cells were better preserved and slightly larger, with more cytoplasm and a more regular nuclear outline. Though still not specific the appearances were now those of proliferating reticulum cells. An occasional (reticulum) cell was in mitosis. (*b*) Eosinophil polymorphonuclear leucocytes were numerous and prominent, forming many large dense aggregations (Figs. 3 and 4). No cells could be distinguished with certainty as eosinophil myelocytes. (*c*) Multinucleated giant cells were more numerous, still without diagnostic features but not unlike osteoclasts (Fig. 5). Appearances otherwise were much the same as before: a small amount of fibroblastic proliferation, many lymphocytes, comparatively few neutrophil 'polymorphs,' and occasional plasma cells.

The disease process appeared to be of the nature of a reticulum cell or histiocytic overgrowth with accompanying inflammatory changes, predominantly as an eosinophil reaction. It brought to mind the so-called eosinophilic granuloma of bone, and this diagnosis was suggested as the most likely. There were no histological findings to suggest neuroblastoma or Wilm's tumour.

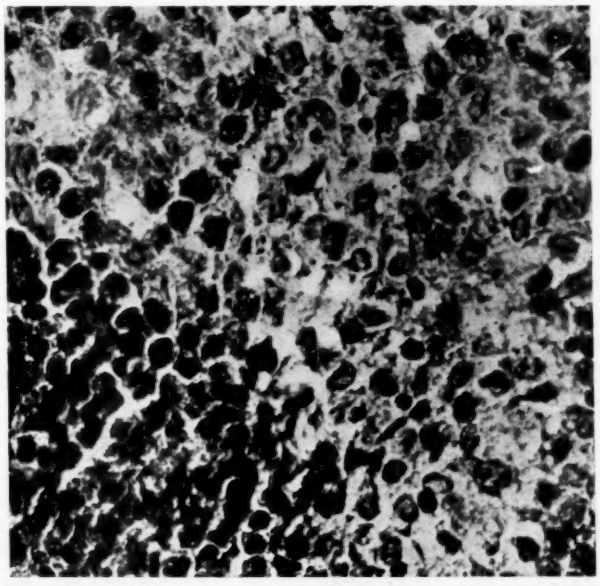

FIG. 4.—High-power view of the same area as in Fig. 3. The dark cells are intensely eosinophilic. The less hyperchromatic cells are of reticulum cell type. ×350.

X-ray examination on Aug. 8, 1947, showed a further area of bone erosion in the occipito-parietal region.

PERIPHERAL BLOOD EXAMINATION:

Total red blood count,	4,480,000 per c.mm.
Total white blood count,	25,800 per c.mm.
Neutrophil polymorphs	50% = 12,900 per c.mm.
Eosinophil polymorphs	4% = 1,032 per c.mm.
Basophil polymorphs	nil
Large lymphocytes	4% = 1,032 per c.mm.
Small lymphocytes	40% = 10,320 per c.mm.
Monocytes	2% = 516 per c.mm.

Individual erythrocytes and leucocytes showed no abnormalities. No primitive cells were seen. The figures indicated a general leucocytosis and a slight absolute eosinophilia.

BIOPSY OF STERNAL BONE MARROW. The material consisted of cellular tissue with cells of the erythroid and granular series present in average normal proportion. Erythropoiesis was normoblastic and no megaloblasts were seen. Eosinophil myelocytes were a little more numerous than usual. Megakaryocytes were plentiful. There were no abnormal cells, and no indication of any leukaemic process, myeloma, or other neoplasm.

BLOOD CHEMISTRY:

Blood cholesterol, 118 mg. %.
Blood phosphorus, 3·5 mg. %.

X-ray examination of all bones on Aug. 9, 1947, showed areas of irregular absorption and erosion in the left iliac bone, the left mastoid and orbital regions, and in the occipito-parietal region (Fig. 6).

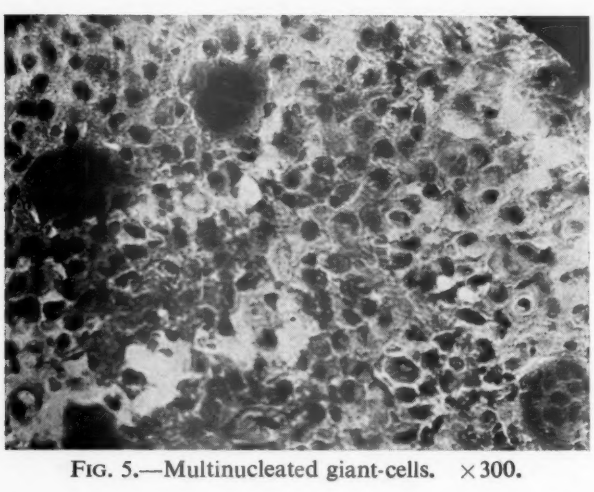

FIG. 5.—Multinucleated giant-cells. ×300.

An irregular pyrexia had continued since admission to hospital, and the general condition of the patient had deteriorated steadily. The petechial rash spread up the left side of the neck and head, and there was slight enlargement of the lymph nodes of both sides of the neck. No treatment, including the full course of penicillin, had produced any improvement. The baby died on Aug. 12, 1947.

A full post-mortem examination was made by Dr. W. P. Weir of the Western Infirmary, Glasgow,

FIG. 6.—Irregular erosion and absorption in the left iliac bone.

who is reporting his findings in a separate article in preparation. He has kindly allowed us to make use of his notes.

The macroscopic findings included enlargement of the spleen, areas of tumour-like growth in the left vertex, left mastoid region, and in the wing of the left ilium, but no gross abnormality in the lungs, thymus, mediastinal, and abdominal lymph nodes.

Microscopically, abnormal reticulum cell proliferation, focal and diffuse, could be seen in the lymph nodes, lungs, skin, one of the lesions in bone, and especially in the spleen. Besides this, some areas of the lesions in bone still retained the appearances of eosinophilic granuloma. It was not until the tissues obtained at necropsy were examined microscopically, and the findings, together with the clinical data, compared with previous accounts in the literature, that Letterer-Siwe disease was diagnosed. Seen in retrospect the clinico-pathological syndrome presented by this patient was an almost typical example of the condition.

Discussion

Mallory (1942) and Jaffe and Lichtenstein (1944) have given full descriptions and discussions of Letterer-Siwe disease and its relationship to the group of reticulo-endothelioses, Schüller-Christian disease, and eosinophilic granuloma of bone, and only a short outline of current views will be given here.

Abt and Denenholz (1936) made six categories of the disorders of the reticulo-endothelial system.

Lipoid storage diseases (Schüller-Christian, Niemann-Pick, and Gaucher diseases), certain leukaemias, neoplasms such as reticulum cell sarcoma, and Hodgkin's disease made up four of the categories. The remaining two were first, reticulo-endothelial hyperplasias where acute infection, presumably primary and causal, was present; and secondly, reticulo-endothelial hyperplasias where there was no obviously related infection. The non-infective category comprised Letterer-Siwe disease. Wallgren (1940) considered that the last two categories were in fact identical and that infection played no part in the aetiology. Further, he drew attention to the close relationship of Letterer-Siwe disease to Schüller-Christian disease and described two illustrative clinical examples. The first in his opinion was 'intermediate between so-called infectious reticulo-endotheliosis and Letterer-Siwe disease,' and the second intermediate 'between the latter malady and Schüller-Christian disease.' He gave a list of 23 reported cases, each an example of infectious reticulo-endotheliosis or Letterer-Siwe disease or Schüller-Christian disease, and arranged them in order according to their duration. In this way he showed that there were many transitional types between one disease and the others, and he stated that neither Letterer-Siwe disease nor Schüller-Christian disease had any characteristic feature that could not occur in the other. The relationship between these two diseases had been noted as well by Flori and Parenti (1937) and by Glanzmann (1940). In the year after Wallgren's observations Farber (1941) also drew attention to the close relationship and made two further contributions to the pathology of the underlying disorder. First, he was unwilling to accept Schüller-Christian disease as belonging to the group of simple lipoid storage diseases; secondly, he related both Letterer-Siwe disease and Schüller-Christian disease to the so-called eosinophilic granuloma of bone, remarking that all three were conditions which 'represent variations in degree, stage of involvement, and localization of the same basic disease process.'

It would be appropriate to make a few remarks here on 'eosinophilic granuloma of bone,' an uncommon condition which has not received much publicity in Great Britain up to date, but is a condition which is important when it arises because of its simulation of a malignant tumour despite an entirely favourable prognosis.

The condition was originally described by Otani and Ehrlich (1940) and Lichtenstein and Jaffe (1940) independently. It is a circumscribed destructive lesion of bone, occurring usually in children or adolescents and sometimes in young adults, monostotic or polyostotic in distribution, and liable to affect almost any bone other than those of the hands and feet. There may or may not be localizing symptoms, expansion of the bone or fracture. Jaffe and Lichtenstein (1944) stated that there was nothing distinctive about the radiological appearances of the individual lesion, an area of rarefaction, generally oval or circular (often with a punched-out appearance when in the calvarium), starting in the interior of a bone and growing, usually rather rapidly, to involve the cortex which may become perforated. In different cases the findings may simulate osteomyelitis, primary bone neoplasm, multiple myeloma, Ewing's tumour, a metastasizing carcinoma, or Schüller-Christian disease. Histologically the lesion is characterized by sheets of proliferating histiocytic cells with which are mingled varying numbers of eosinophil leucocytes and scattered multinucleated giant cells. The prognosis with regard to healing of the individual lesion is good: 'The lesions do not tend to become scarified, collagenized and lipidized, heal rapidly after simple curettage even without supplementary roentgen irradiation of the site, and may indeed heal by resolution even without any therapeutic intervention whatever' (Jaffe and Lichtenstein, 1944).

Both Wallgren's contentions, mentioned above, have been accepted by authorities on the subject. Thus Mallory (1942) has agreed that Schüller-Christian disease is not of the lipoid-storage group of diseases but a manifestation of the same granulomatous process that underlies Letterer-Siwe disease. According to Jaffe and Lichtenstein (1944) '. . . it is not Schüller-Christian disease but only xanthoma tuberosum multiplex that constitutes the cholesterol lipid disorder analogue of Gaucher's disease and Niemann-Pick disease.' Mallory and Jaffe and Lichtenstein again agree in adding eosinophilic granuloma of bone as a further clinical expression of the same disorder, a reticulo-endothelial granulomatosis varying in distribution within the body and of uncertain aetiology.

Of the different manifestations of the disorder, Letterer-Siwe disease, with its widespread lesions and fatal course, is usually well defined; eosinophilic granuloma of bone, with its restricted skeletal localization and favourable prognosis, is also usually well defined; whereas Schüller-Christian disease is still a rather miscellaneous group. To quote yet again from the later article of Jaffe and Lichtenstein (1944), they have said '. . . on the one hand, in the early stages of evolution of Letterer-Siwe disease one may find destructive skeletal lesions resembling cytologically those of eosinophilic granuloma of bone, and, on the other hand, in its chronic stages Letterer-Siwe disease takes on the aspect of Schüller-Christian disease, the skeletal and even certain visceral lesions undergoing lipogranulomatous transformation.' This means that the classification on histological grounds of a given example of the disorder may be difficult, and the literature contains many accounts of illustrative transitional types (Guizetti (1931), Merritt and Paige (1933), Grady and Stewart (1934), Hertzog, Anderson, and Beebe (1940), Curtis and Cawley (1947), Weinstein, Francis, and Sprofkin (1947)). Clinically, however, there is a broad correlation of the different disease groups

with age, and Mallory (1942) has summarized the position clearly (p. 956) as follows:

> 'Strongly suggestive evidence therefore lies at hand that all these various syndromes represent a single entity—rapidly fatal in the infantile forms, which have been described as Letterer-Siwe's disease and reticulo-endotheliosis; chronic, but still of serious import because of the likelihood of cerebral and hypophyseal involvement, in early childhood (Hand-Schüller-Christian's disease); and comparatively benign in later childhood or in the adult, where the usual picture is that of eosinophilic granuloma. Proof of this identity must of course await the discovery of the etiology.'

The aetiology of Letterer-Siwe disease and of the other variants of systemic reticulo-endothelial granulomatosis is still unknown. The possibilities appear to be an endogenous metabolic disturbance, a specific infection, or varying behaviour of a neoplastic process. Van Creveld and Ter Poorten (1935) thought that infection was probably primary and causal though they did mention the possibility of its being secondary and sequential. Wallgren (1940) thought that infection played no part at all in the aetiology. Mallory and Jaffe and Lichtenstein have expressed the opinion that the condition is an inflammatory histiocytosis arising in response to some as yet unknown specific infectious agency, though attempts to isolate bacterial organisms or a virus have not succeeded so far. No attempt was made to isolate organisms or virus from our patient. All we can say is that if there was an organismal cause the organism concerned was not affected by some 4,000,000 units of penicillin given over a period of 17 days.

Summary

An example of acute reticulosis of infants (Letterer-Siwe disease) is described.

A short summary is given of current views on the inter-relationships and probable underlying identity of this condition with 'infective' reticulo-endotheliosis, Hand-Schüller-Christian disease, and eosinophilic granuloma of bone.

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CASE REPORT

MECONIUM ILEUS WITH NO PANCREATIC ABNORMALITY

BY

E. HINDEN, M.D.(Camb.), M.R.C.P.(Lond.)

(RECEIVED FOR PUBLICATION, JULY 16, 1949.)

Jennifer W., born on February 20, 1949, was the second child of healthy parents; the first child is quite well, and this pregnancy, labour, and delivery were quite normal.

Case Report

The infant had vomited about two hours after delivery, and continuously since, and there was no bowel action for the first forty-eight hours. She was then sent to Whipps Cross Hospital with the presumptive diagnosis of intestinal obstruction.

On admission the baby was in fair condition; dehydration was not marked. She was still continually vomiting bile-stained material. A straight radiograph of the abdomen showed that the gas-filled intestine ended abruptly in the left iliac fossa. This was interpreted as an obstruction at the junction of the descending and sigmoid colons. At operation that evening (Mr. S. G. Nardell) the abdomen was found to contain free yellow fluid. The small bowel was congested and grossly distended with fluid and gas to within a few inches of the ileo-caecal valve, after which point the intestinal contents changed to hard, putty-like meconium. The caecum and large intestine were collapsed and minute, the caecum about the size of a thumb-nail, and the colon about as thick as a matchstick. There was a volvulus of the whole of the small intestine so that the caecum lay in the left iliac fossa, and the gas-filled bowel, which was thought to be the descending colon, was in fact the small intestine leading to the caecum. The operator noticed, however, that the contents of the ileum could be forced onwards into the narrow caecum and colon, though with some difficulty. The anatomy of the parts was restored and the abdomen closed.

The baby was treated with intravenous fluids and continuous gastric suction, and had a very stormy forty-eight hours post-operatively. Then the bowels acted and meconium was freely discharged for the next twenty-four hours. The baby picked up and ultimately did very well. Her weight on February 28 (six days after operation), was 6 lb. 4 oz.; on discharge six weeks later it was 8 lb. 5 oz.

It is considered nowadays that meconium ileus is due to cystic fibrosis of the pancreas. With this diagnosis in mind, the baby's faeces were examined for trypsin. Analysis on February 25 showed that trypsin was present (by the x-ray film gelatin test) to a dilution of 1:20, and on March 14 to 1:640. These figures contradicted a diagnosis of pancreatic disease.

The baby did well at home for about a fortnight. On April 26 she sickened with gastro-enteritis, and was admitted to Plaistow Fever Hospital. There was no abdominal distension at that time. She was treated with subcutaneous and intragastric fluid drips, but the latter was not retained. Bowel action ceased abruptly on the morning of April 28, and gaseous distension began; she had a very small yellow stool on the following day after a glycerine suppository. Vomiting worsened, and she was admitted that day to Whipps Cross Hospital, again suffering from intestinal obstruction; it seemed likely that this was due to adhesions following the operation. The surgeon advised conservative treatment, gastric drainage and intravenous fluids, and the baby responded. Her bowels started working again, and on May 4 she was being fed by mouth and had normal motions, but on May 6 she suffered a sudden relapse of the enteritis, and died that day.

Discussion

At the post-mortem examination the following day all the organs were seen to be macroscopically normal except the intestines. The small gut was congested and of normal calibre. All the coils were matted together, and the gut was adherent to the operation scar; the mucosa appeared normal. No obstruction could be found. The large gut was collapsed, gradually narrowing from a normal caecum, which was matted to the coils of the small intestine. Microscopically, the pancreas appeared normal, apart from early post-mortem change. The liver showed very early fatty infiltration, and the intestine petechial haemorrhages throughout the muscle coat, the red cells appearing quite fresh. In addition the whole wall was infiltrated by chronic inflammatory cells, mostly histiocytic-like in character, a small proportion of plasma cells and eosinophils also being present.

The findings at operation were exactly as described by Andersen (1946) in meconium ileus, even to the complicating volvulus. In this disease, usually due to insufficient pancreatic digestion, the meconium is too hard and too dry to be passed normally, thus causing a mechanical obstruction. In this patient, however, the pancreas was quite normal.

This uncommon finding questions the accuracy of the diagnosis. Farber (1944) mentions that occasionally inspissated meconium may be found in intestines obstructed for other reasons, for example, by stenosis of the ileo-caecal valve or volvulus, but in those circumstances it readily clears itself if the obstruction is removed. Could this infant have been suffering from a congenital volvulus ? I think not, for the following reasons.

Barrington-Ward (1937), quoting Dott, writes:

'The brunt of the obstruction at first falls on the third part of the duodenum,' and, 'since the involved bowel has a free exit below to the colon, it does not become distended, but collapsed.' In this case, the duodenum was normal, the bowel was distended, and had not emptied itself into the colon, although there was no anatomical disturbance in the region where the bowel narrowed. Ladd and Gross (1941) agree with these two points. They state that as a rule symptoms do not arise during the first days of life, and some meconium is passed or is obtained by enema. Neither observation was true of this patient. They go on to say that when a true congenital volvulus is relieved, it is impossible to restore the normal anatomy, for the caecum and all the colon will remain on the left. Here, however, after reducing the twist, the operator easily replaced the caecum and ascending colon on the right of the abdomen. Plainly, this was not a congenital volvulus. It seems likely that the minor volvulus was due to the over-activity of a normal small gut. Adamson and Hild (1939) report a fatality from meconium ileus, in which an ileocolic intussusception was found after death; this they ascribe to excessive peristalsis.

It was hoped at first that the baby would join the very small band of infants who have survived a meconium ileus, but having battled through the hazards of a second intestinal obstruction, she succumbed to gastro-enteritis.

I gratefully acknowledge the assistance of my colleagues at the two hospitals, and their permission to publish their findings.

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